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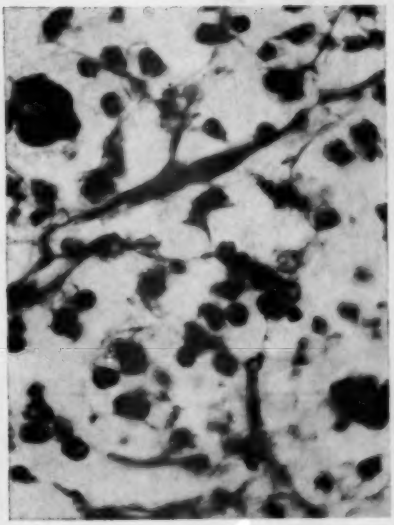

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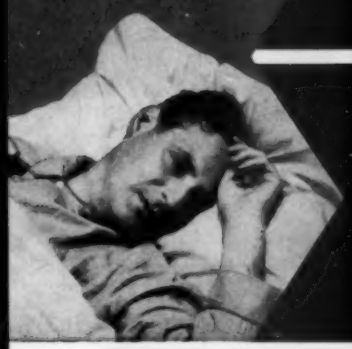

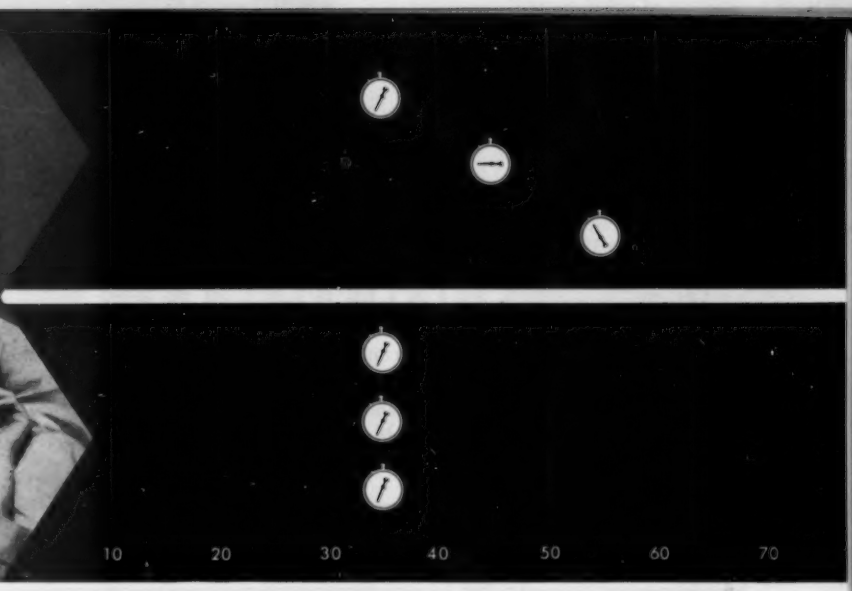

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The Influence of Cortisone upon Protein Metabolism

PAUL R. CANNON, M.D.
LAURENCE E. FRAZIER, M.S.
and
RANDOLPH H. HUGHES, Chicago

Cortisone is often referred to as a "catabolic" agent because of the fact that, when administered in sufficiently high dosage, it causes tissue breakdown and an increased urinary loss of nonprotein nitrogen. The accompanying impairment of tissue synthesis is evidenced by a retardation of growth, a negative nitrogen balance, a lessened capacity to heal wounds or to form antibodies, and a diminished inflammatory response. Simultaneously there is glycosuria, increased glycogenic deposition in the liver, and marked resistance to insulin. The latter effects are thought to be due, in part, to the conversion of carbon residues of amino acids released from the tissues into glycogen. Thus, despite a widespread distribution of amino acids available for tissue synthesis, these are presumably not present in proper amounts and suitable proportions for many of the exacting needs of protein synthesis.

Evidence supplying a basis for the catabolic point of view stems from the early experiments of Long, Katzin, and Fry, in which it was demonstrated in fasting rats that injections of adrenal cortical extract caused an accelerated output of nonprotein nitrogen and a marked accumulation of glycogen in the liver.[1] Later it was shown, also, that subcutaneous injections of cortisone into adrenalized rats brought about similar effects[2]; and Ingle and associates found that the administration of cortisone to liverless rats caused a rise in the plasma amino acids.[3] Moreover, Hoberman showed in adrenalectomized rats an increased rate of conversion of body proteins to amino acids and an accelerated breakdown of amino acids as well.[4] In further explanation of some of these effects Cagan and associates reported that patients with Addison's disease displayed a decreased capacity to metabolize intravenously administered amino acids.[5] To explain this they suggested that the accelerated catabolism induced by cortisone may be accomplished by oxidative systems concerned with the deamination of amino acids. Histochemical studies in cortisone-treated animals have also revealed a loss of ribonucleic acid in liver cells as evidenced by a diminution in cytoplasmic basophilia.[6] Assuming that protein synthesis occurs at least to a considerable extent in mitochondria and microsomes, this loss could account for some impairment of protein synthesis.

Of further interest is the fact that the administration of cortisone may be associated with a loss of nitrogen from some tissues and a concomitant gain in others.[2] For example, it has been reported that there may

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The Department of Pathology, the University of Chicago.

This work was done in cooperation with the U. S. Navy, Office of Naval Research. The Douglas Smith Foundation for Medical Research of the University of Chicago also cooperated in this study.

be an increase in the total amount of ribonucleic acid in the liver in association with an active production of plasma proteins, whereas simultaneously nitrogen is lost from striated muscle and other carcass fractions. Chow has found, moreover, that cortisone may induce an increase in arginase activity in the liver, a decrease in amylase activity, and a rise in total liver nitrogen.[7] In view of these and other facts, Roberts has suggested that adrenal cortical secretions act mainly to effect the labilization of tissue proteins, thus ensuring their translocation, particularly to the liver, for reconversion into plasma proteins.[8] It should be noted, moreover, that at times cortisone may accelerate the urinary loss of potassium, and in view of the essentiality of this ion in tissue synthesis,[9] such a loss might further hamper the processes of tissue synthesis.

All of these facts suggest that cortisone may effect a disturbance in the dynamic equilibrium between the forces of anabolism and catabolism, as a result of which an accelerated catabolism promotes the release of amino acids and, at the same time, the steroid induces an augmentation of the processes of gluconeogenesis. Intermediate metabolism is thus deviated to some degree from the synthesis of protein to that of carbohydrate and fat.

Another point of view has been proposed by Albright, viz., that cortisone and related adrenal steroids act primarily as inhibitors of tissue protein synthesis.[10] Albright made this suggestion because of his observations that patients with symptoms of hypercorticoadrenalism (Cushing's disease) often tended to remain in positive nitrogen balance. Experimental support for this concept has come from Clark, who found that, following the ingestion of isotopic amino acetic acid (N^{15}) in conjunction with the administration of cortisone, an increased excretion of isotope ensued, this factor suggesting an antianabolic action through the retarded utilization of exogenous protein rather than because of a breakdown of the tissues themselves.[11]

In these two points of view, therefore, a choice is presented between a primary catabolic action with an indirect impairment of tissue synthesis and a directly antianabolic effect upon tissue synthesis itself. In any case, and regardless of the mechanism of action of cortisone, it is important to characterize its action as completely as this can be done because of the possibility of attainment of a metabolic counteraction of exaggerated adrenal cortical hormonal effects, by anabolic or anticatabolic measures. Among these might be considered the use of pituitary somatotrophic hormone, testosterone, vitamins, insulin, thyroid hormone, high protein intake, and possibly other measures.

For the study of some of these questions the following experiments were performed, using as experimental animals both normal and protein-depleted rats. The latter types of animals are especially useful in studying the relationships of potassium to cortisone action due to the fact that during the course of depletion the rats lose both nitrogen and potassium. In the processes of repletion, in consequence, the role of potassium in relation to cortisone action can be readily ascertained. The question whether cortisone may induce a loss of potassium was studied by means of flame photometry on specimens of urine and feces, and by histologic examinations of heart muscle for evidences of the development of lesions characteristic of potassium deficiency.

MATERIALS AND METHODS

Adult male albino rats of the Sprague-Dawley strain were used. Those used for purposes of protein repletion had been previously subjected to protein depletion by a method described.[12] The "standard ration" used for repletion was of the following composition:

Dextrin	69.5%
Corn oil	4.0%
Cellulose	7.5%
Salt mixture (free of potassium)	5.0%
Vitamin mixture	1.5%
Fibrin	15.07%
Choline, 50%	0.9 ml.
Water	11.0 ml.
Percomorph liver oil	0.45 ml.
Potassium chloride	0.10%

Dried beef fibrin (Wilson Laboratories) was used because it is a high-quality protein which is also practically devoid of potassium. The "standard ration" when fed in daily amounts of 11.5 or 13 gm. per rat, depending upon its moisture content, supplied a caloric intake of approximately 37 cal.,

10 mg. of potassium salt, and adequate amounts of all other dietary constituents essential for an effective over-all tissue protein synthesis. Protein-depleted rats fed this ration made a steady average weight gain, over a 16- to 24-day repletion period, of about 2 gm. per day. The animals from here on will be referred to simply as "depleted." The vitamin mixture contained nicotinamide, calcium pantothenate, pyridoxine hydrochloride, riboflavin, and thiamine hydrochloride.

In the following eight experiments attempts were made to answer the following questions:

1. Is the action of cortisone in the intact animal predominantly catabolic or antianabolic?

ated weight loss and an increased output of urinary nitrogen subsequent to the addition of cortisone to a nitrogen-free ration would indicate an additive effect with respect to the existent catabolism.

For the testing of this supposition four groups of rats were fed the standard ration devoid of fibrin over a period of 17 days. Ten of the animals (two groups of five each) were protein-depleted; the other eight (two groups of four each) were normal animals. One group of animals in each category received 3 mg. of cortisone acetate per rat daily in the ration. The animals were weighed

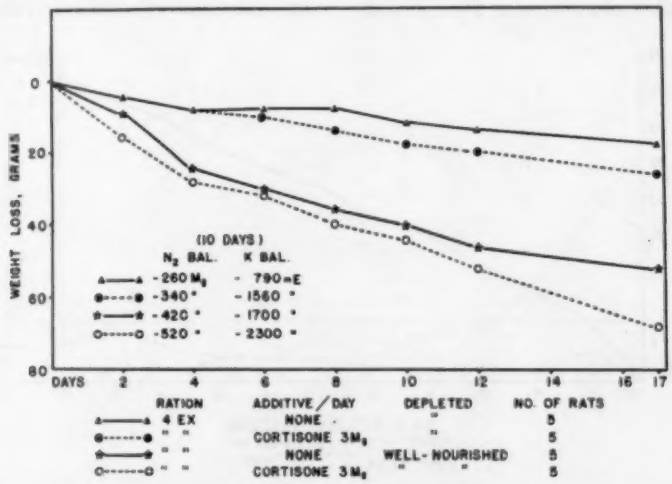

Fig. 1.—Average weight curves for rats fed a fibrin-free ration, with and without cortisone. Note the greater weight loss in each group receiving cortisone as well as an increased negative nitrogen and potassium balance.

2. In what ways does cortisone act to inhibit over-all tissue synthesis as measured by its effect upon protein repletion?
3. Does a lack or deficiency of potassium influence the inhibition by cortisone of protein metabolism?
4. Does ascorbic acid or some of the B vitamins have a capacity to lessen the inhibitive effects of cortisone upon protein metabolism?
5. Can caloric increases alone counteract the inhibitive effects of cortisone upon tissue synthesis?

EXPERIMENT 1.—If the net effect of cortisone is catabolic, its degradative action should heighten an existent state of catabolism, as, for example, in one induced by the feeding of a nitrogen-free ration. Thus an accelerfrequently throughout the period of observation, and nitrogen balances were determined for the final 10 days. All of the rats ate the rations practically completely from day to day, thus ensuring complete ingestion of the cortisone. The results, in terms of average weight losses and nitrogen balances, are shown in Figure 1, where it is seen that the weight losses for the animals receiving cortisone were consistently greater than those of the rats eating the nitrogen-free ration alone. Similar differences obtained with respect to nitrogen balance: viz., nitrogen excretion in both categories was greater in the cortisone-treated animals. Potassium balances were

also determined, and these paralleled those for nitrogen.

These evidences of an acceleration of two important features of the catabolic state coincident with the ingestion of cortisone suggest, therefore, that under these experimental conditions the action of the steroid was presumably catabolic.

EXPERIMENT 2.—In the second experiment the response to protein repletion was compared in two groups of depleted rats fed identical "standard" rations, but with the animals in one group also receiving daily subcutaneous injections of cortisone acetate (5 mg.). The animals were kept in individual cages, nine in the control group and eight in the cortisone-treated group. Throughout the experiment, which extended over a period of 24 days, individual food consumption was essentially complete for all animals, thus demonstrating that the injections of cortisone did not diminish appetite. Nevertheless, the averaged weight gains (Figure 2) reveal clearly the inability of the cortisone-treated animals to utilize the ration effectively for purposes of over-all tissue protein repletion. As evidence for this, their weights remained practically stationary despite the continued daily ingestion of all dietary essentials adequate, in the absence of cortisone administration, for effective protein repletion.

After nine days of cortisone administration, three of the animals received in the ration an additional amount of potassium chloride (181 mg. per day) in order to determine whether an increased intake of potassium might help them to overcome the inhibitive effects of cortisone. However, in the ensuing six days no improvement resulted (Figure 3). Evidently, therefore, the inhibition of tissue synthesis under the influence of cortisone could not be accounted for on the basis of an inadequate intake of potassium. Cortisone injections were then stopped; during the following six days protein repletion lagged, followed by a sudden resumption of weight gains similar to those observed in the control animals, and indicating that with time the inhibitive action of cortisone had vanished. Throughout the experiment dietary consumption from day to day was complete in all animals of both groups.

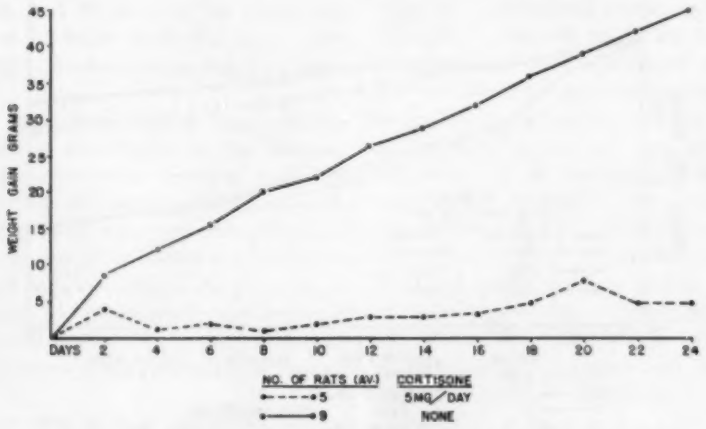

Fig. 2.—Average weight curves for depleted rats fed identical rations but with those in one group receiving daily injections of cortisone acetate. Note the practically complete absence of weight gain in the latter animals, despite the complete daily ingestion of the rations.

EXPERIMENT 3.—In a third experiment the daily intake of potassium chloride for each rat was reduced to 5 mg., while the ration was fed as before to two groups of depleted rats, four animals in each group. Over a 10-day period of repletion the inhibitive effect of cortisone was again evident,

the control rats making average weight gains of 30 gm. per rat in contrast to gains of only 3 gm. per rat with respect to the cortisone-treated animals. Histologic examinations of the hearts, however, failed to reveal any lesions indicative of potassium deficiency. It is apparent, therefore, that even with an extremely low intake of potassium the cortisone inhibition could not be attributed to a critical loss of potassium ion.

EXPERIMENT 4.—Finally, depleted rats, in two groups of four animals each, were fed the standard ration supplemented with sodium chloride at a concentration of 1 gm. per 100 cc. in order to determine whether an added increment of sodium salt might, in conjunction with cortisone, effect a displacement of potassium from cells actively concerned with the processes of tissue synthesis. Again, however, the cortisone inhibition developed as usual, and no myocardial lesions were found on completion of the experiments.

EXPERIMENT 5.—In order to ascertain in a more quantitative manner the extent of nitrogen loss in the course of protein repletion as influenced by the administration of cortisone, balance experiments were performed in depleted rats (eight in all) which were fed the standard ration, but with half of the animals receiving daily subcutaneous injections of cortisone acetate (5 mg.). For five days prior to the start of the experiment all rats were fed the ration devoid of both fibrin and potassium, with determinations of nitrogen and potassium balances on the final two days. The standard ration was then fed in conjunction with two-day collections of urine and feces over a period of eight days.

The results showed that during the preliminary period all rats lost weight and all went into negative nitrogen and potassium balances. When fibrin and potassium were restored to the ration, however, both balances became positive and continued so, except in the cortisone-treated rats, in which the nitrogen and potassium balances terminally became negative, although only slightly so. In short, the effect of the cortisone was definitely to induce negative balances of both nitrogen and potassium.

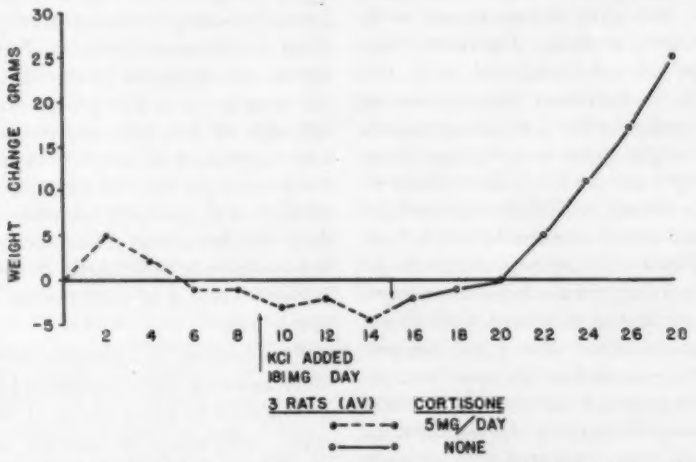

Fig. 3.—Average weight curves of three depleted rats fed the repletion ration and injected daily with cortisone acetate. Note the failure of added potassium intake to modify the inhibitive influence of cortisone upon protein repletion.

EXPERIMENT 6.—It has been suggested that the inhibitive effect of cortisone upon protein metabolism results in part at least from an increased tissue need for cyanocobalamin. For example, experiments by Meites [13] and by Meites and Feng [14] led them to the conclusion that supplementation of the rations of young rats deficient in cyanoco-

balamin caused an increase in appetite, an enhanced availability of carbohydrate and protein in metabolism, and a concomitant counteraction of the inhibitive effects of cortisone upon growth.

In subjecting this idea to further examination we fed depleted rats the standard ration, in four groups of five animals each. The animals in two of the groups received identical repletion rations except that each rat in one group also received a daily supplement of 3γ of cyanocobalamin. All 20 rats were also given daily subcutaneous injections of 5 mg. of cortisone acetate. The animals in the remaining two groups were similarly treated except that each received the rations ad libitum, with daily determinations of the individual amounts eaten. The results, over a 10-day period, were as follows: In the first two groups the daily food consumption was essentially complete for each animal, and the averaged weight gains were similar (from 0.2 to 0.5 gm. per day). In the animals receiving the rations ad libitum the averaged weight gains varied between 0.8 and 1.2 gm. per day. However, food consumption of the animals receiving cyanocobalamin averaged 15.5 gm. per day as compared with 14 gm. for the animals of the other group, suggesting that the cyanocobalamin may have improved their appetites slightly. Nevertheless, the maximal average gain of only about 1.2 gm. per day, when compared with the average gain of 2 gm. per day for rats not receiving cortisone and on a smaller intake of ration daily (13 gm.), clearly indicates that supplementation with cyanocobalamin failed under these conditions to overcome the inhibitive effects of cortisone.

While this experiment was in progress, 10 additional depleted rats were fed a daily ration containing 5 mg. of cortisone acetate and 5 mg. of potassium chloride. Five of the animals also received cyanocobalamin supplements in the amount of 3γ per day. At the end of 17 days the animals were killed and their hearts examined for evidences of focal necroses characteristic of potassium deficiency. Such lesions were found, equally distributed in the animals of the two groups, in 6 of the 10 hearts examined. All of the adrenal glands were also atrophic, thus indicating that the addition to the ration of cyanocobalamin had failed to counteract the effects of the cortisone administration.

In a second experiment two groups of depleted animals, 10 in each group, were again fed the standard ration ad libitum; each rat also received a daily cyanocobalamin supplement in the amount of 4γ. Each animal also received a daily subcutaneous injection of cortisone acetate, 2.5 mg. per day for the first six days, and 4 mg. per day for the final five days. After 11 days of protein repletion weight gains for each group averaged, for the first group, 24.6 gm.; for the group receiving cyanocobalamin, 24.8 gm. Food consumption averaged 17 gm. per day for the animals of the first group and 18 gm. for those of the second group. Nevertheless, although the rats receiving the cyanocobalamin supplement ate slightly more ration on the average per day, the weight gains in each group were essentially identical. It is evident, therefore, that under these conditions cyanocobalamin failed again to overcome the inhibitive action of cortisone in any measurable way.

EXPERIMENT 7.—Because of the possibility, however, that cortisone in high dosages may accelerate tissue losses of certain vitamins, particularly of ascorbic acid, or of certain members of the B group, experiments were performed in which depleted rats were fed cortisone daily in 3 mg. amounts, but with doubled and tripled supplements of the vitamin mixture customarily used in the standard ration. Rats in four groups of five animals so treated were subjected to protein repletion by the feeding of the standard ration. After nine days of repletion it was evident that despite the complete acceptance of the rations by all the animals, there was no evident additive effect from the vitamin supplementation, the average weight gains being identical and all being considerably less than those of animals similarly treated but receiving no cortisone. Similar results were obtained with respect to the feeding of

rations reinforced with ascorbic acid, up to daily intakes of 40 mg. per rat per day.

It is evident, therefore, that under the conditions of these experiments additions to the repletion ration of ascorbic acid or of mixtures of B vitamins had no appreciable influence in lessening the inhibitive effects of cortisone upon tissue protein synthesis.

EXPERIMENT 8.—In the last of the experiments herein reported, the possibility was considered that in the experiments of Meites and Feng an increased food consumption alone may have been responsible for the lessening of the inhibitive effects of cortisone upon tissue synthesis (growth). In order to test this possibility isocaloric rations were fed to groups of depleted rats, with each ration containing identical amounts of cortisone acetate but with the caloric supplements composed of carbohydrate, protein, or fat. Four groups of rats were fed the standard ration containing 3 mg. of cortisone acetate per day. After receiving this ration for four days, the animals were treated as follows: One group continued to eat the ration; to each ration of the remaining three groups a caloric supplement of 12 cal. was added in the form of dextrin, beef fibrin, or corn oil. Consumption of the rations continued essentially complete from day to day so that over a period of 18 days each animal received an identical intake of cortisone and of dietary essentials, differing only in the fact that the rats in the three latter groups received additional calories in the form of carbohydrate, protein, or fat. At the end of the experiment all animals were killed, and carcass analyses were done in order to compare those with analyses done on protein-depleted rats which had been killed at the beginning of the experiment.

The results of this experiment were noteworthy in that from the start of caloric supplementation all animals gained weight more rapidly than did those on the standard ration. It was quickly apparent, moreover, that added calories alone counteracted some of the inhibitive effects of cortisone upon weight gains. At the end of the 18 days, all animals of the three groups had gained considerably more weight than had those on the standard 37 cal. ration. However, the carcass analyses revealed the fact that the increased weights were due not to an increased deposition of tissue protein but rather to an increased deposition of fat. In short, protein supplementation had merely supplied additional material for gluconeogenesis and ultimate conversion into fatty tissue. A repetition of this experiment yielded similar results.

COMMENT

It is of particular interest that in relation to the demonstration of an inhibitive effect of cortisone upon tissue protein synthesis, there was no indication of toxicity such as might have been evidenced by a loss of appetite. This fact is well known, however, in human subjects treated with cortisone or corticotropin, and, indeed, these materials are often used in order to improve appetite. Furthermore, in the experiments in which additional calories were supplied to the rats receiving cortisone, as, for example, supplements of fibrin alone, the conversion of the extra protein into fat suggests that the metabolic deviation may be related in some way to a demand for the conservation of energy. Such a tendency was first noted by Long, Katzin, and Fry, in that, following the administration of glucose by stomach tube, there was a decreased urinary loss of nitrogen in comparison with that which ordinarily accompanied injections of adrenal cortical extract. Engel and associates later confirmed this finding in nephrectomized rats in the demonstrations of a diminished accumulation of urea after the injection of adrenal cortical extract and dextrose. They also observed a similar effect accompanying the intravenous injection of amino acids, but not of protein or of a fat emulsion.[15] According to Engel: "It would appear then that the metabolic mixture available at the time of hormone action plays a decisive role in determining the metabolic response to adrenal hormone. In certain respects it seems as if the organism is aware of the value of this adjustment

for if it is given a choice in the matter it attempts to prevent undue loss of body protein by increasing its appetite and food intake." [16] Similar findings have been reported by Kochakian and Robertson following the administration of cortisone in mice,[17] and by Pearson and Eliel in a patient receiving corticotropin.[18]

In arriving at a decision as to whether the action of cortisone upon protein metabolism is catabolic or antianabolic, further consideration should be given to the question of terminology. For example, ordinarily when the effects of cortisone, adrenal extract, or corticotropin have been termed "catabolic," this has been with reference to such associated events as negative nitrogen balance, loss of weight, failure of growth, lymphocytolysis, etc. Likewise, when Albright suggested that the action of adrenal corticoids might be "antianabolic," he had in mind the persistence of a positive nitrogen balance in certain patients with symptoms of hypercorticoadrenalism. More recently, however, the terms anabolism and catabolism have been applied in a much more restricted sense to various aspects of protein and amino acid metabolism. This has led to some confusion, at least to the extent that terms applicable to the general action of adrenal corticoids have also been applied to specific modes of action at the cellular level or in relation to the actions of specific enzymes.

Using the term catabolism in the general sense, it is evident in the experiments here reported that cortisone acted catabolically to increase the urinary loss of nitrogen and potassium and to restrict the over-all tissue protein synthesis. As has already been pointed out, however, this does not controvert the fact that in the processes of so-called labilization and translocation of protein, localized protein synthesis may occur, as, for example, in the liver. Several workers have suggested that the principal function of the adrenal glucocorticoids may be to reestablish homeostatic mechanisms which have become imbalanced under the influence of stresses of various sorts. According to this latter point of view, amino acids might be shifted from regions of tissue breakdown to regions of tissue synthesis, with the processes of gluconeogenesis acting to convert amino acid residues, which may not immediately be utilizable for conversion into tissue protein, into glycogen or fat.

By whatever mechanism cortisone may have functioned in these experiments, it is evident that its inhibitive or deviating effects upon tissue protein synthesis were not appreciably modified by augmented intakes of ascorbic acid, or of certain of the B vitamins, including cyanocobalamin. Neither were they altered by a lack of potassium ion.

SUMMARY

In the experiments here reported an effort was made to clarify some of the aspects of cortisone action relating to protein metabolism, employing for the most part the method of protein repletion of protein-depleted adult male albino rats as an indication of over-all tissue protein synthesis. Using the term catabolism in a general sense, viz., in relation to a trend toward a negative nitrogen balance and an inhibition of tissue protein synthesis, it is evident that in these experiments cortisone acted as a catabolic agent to inhibit tissue protein synthesis. The inhibitive effect, moreover, was not modified by dietary supplementation with ascorbic acid or with certain of the B vitamins, including cyanocobalamin. Caloric supplementation in the course of protein repletion favored weight gain, but carcass analysis indicated that this was due, not to an increased deposition of tissue nitrogen as a whole, but rather to an increased deposition of carbohydrate and fat. Although attempts were made to ascertain whether or not potassium ion might play a possible role as a limiting factor in relation to the inhibitive action of cortisone, no evidence was obtained indicating that this was the case. Despite the fact that cortisone acted to divert dietary protein from its usual role in the synthesis of depleted tissues, the absence of any evidences of toxicity, such as might have been indicated by a depression of appetite, coupled with the evidence of a conservation of carbohydrate and fat, suggests

that its function under such circumstances may have been to reestablish homeostatic mechanisms which had become imbalanced. In the course of tissue breakdown protein derivatives may be translocated to certain tissues, whereas amino acid residues not immediately utilizable for purposes of tissue protein synthesis may, by the processes of gluconeogenesis, be converted into glycogen and fat.

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Obesity and Degenerative Joint Disease

Experiments in "Yellow" Mice

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Obesity has long been incriminated as an etiologic factor in human osteoarthritis.* In order to test this contention experimentally and in continuation of previous investigations on the effect of nutritional factors on aging joints,† the problem was approached at this time with the use of "yellow" mice, which seem particularly suited for this purpose. This strain is represented by two genotypes differing in regard to only one gene, the Y′ gene, which is present in the one and absent in the other. Bearers of the Y′ gene are yellow-coated and become obese if fed enriched diets; mice not carrying this gene are gray-coated and do not become obese if fed correspondingly. Gray-coated nonobese mice may thus conveniently be used as controls for the study of effects of overweight in their obese littermates.

MATERIAL AND METHODS

Three hundred forty-four gray-coated and yellow-coated male and virgin female mice of strain YBR/Wi were, from the time of weaning on, fed the following diets: (*a*) a stock diet of Purina Laboratory Chow; (*b*) a high-fat diet; (*c*) a high-carbohydrate diet.

Purina Laboratory Chow served as the stock diet and as the base for the high-fat and high-carbohydrate rations. Details of the preparation and composition of these diets have been given previously.[5] These are their main constituents:

	Gm.	Cal./Gm.
Stock diet		
Protein	26.2	3.5
Fat	5.4	
Carbohydrate	48.5	
High-fat diet		
Base	75.0	4.6
Lard (Swift's Silverleaf Brand)	20.0	
Lactalbumin	5.0	
High-carbohydrate diet		
Base	60.0	3.7
Cornstarch	36.0	
Lactalbumin	4.0	

TABLE 1.—*Distribution of Mice in the Various Groups*

Coat Color	Sex	Total No. of Mice	No. of Mice: Stock Diet	No. of Mice: High-Fat Diet	No. of Mice: High-Carbohydrate Diet
Gray	M	91	36	21	34
Yellow	M	79	33	22	24
Gray	F	85	27	28	30
Yellow	F	89	33	26	30
Total		344	129	97	118

The rations were fed ad libitum with water available at all times. The distribution of the animals in the various experimental groups is given in Table 1.

Body weights were taken at weekly intervals. As a rule, the mean weights of the animals kept within a cage were determined. However, if among individual mice differences in weight exceeded 4 gm., the individual weights were recorded. This was necessary especially in yellow-coated females, in which body weights showed marked variations, in particular under the influence of the enriched diets.

The animals were permitted to live to the end of their lives, and they were killed only when found in poor condition. At necropsy, the tibiae and femurs were removed as a whole, decalcified in Bouin's solution, and embedded in paraffin, and slides stained with hematoxylin and eosin were studied microscopically. A number of vertebral columns were also examined.

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* References 1 and 2.

† References 3 and 4.

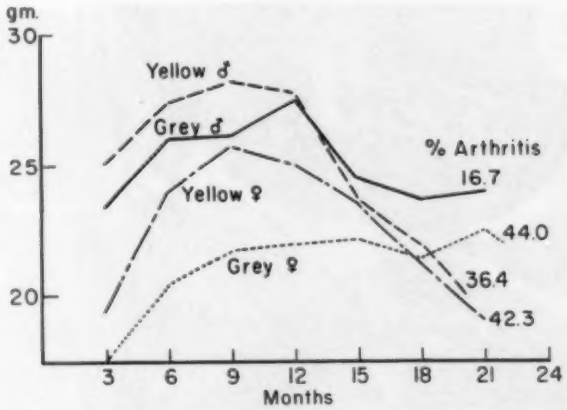


Chart 1.—Mean weight and incidence of degenerative joint disease in "yellow" mice fed a stock diet through life.

OBSERVATIONS

1. *Life Span and Body Weights.*—Details of weights and life span of animals of this strain have been reported previously.[5] The mean weight curves are demonstrated in Charts 1, 2, and 3. As seen from the latter, neither diet caused obesity in gray-coated mice, although overweight up to 10% was noted in females consuming the high-fat ration. The enriched diets induced considerable obesity in yellow-coated mice. The high-fat ration was more effective in this respect than the high-carbohydrate ration, and females were more susceptible than males.

2. *Major Diseases.*—At necropsy and subsequent microscopic examination a variety of visceral lesions were found. The commonest were ophthalmitis, pyelitis, pyelonephritis, amyloidosis, aortitis, myocarditis, hypertrophy of the islets of Langerhans in the pancreas, and endometrial hyperplasia. In

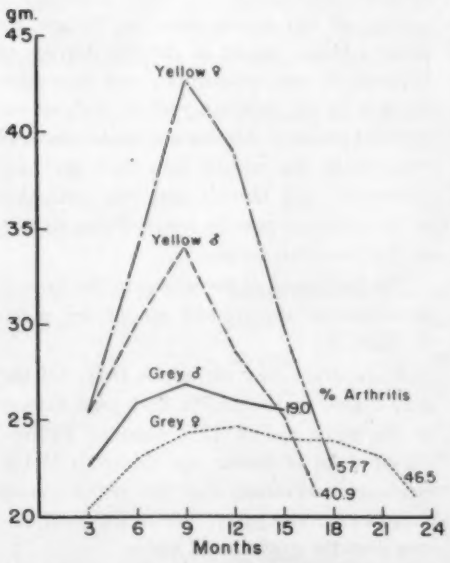


Chart 2.—Mean weight and incidence of degenerative joint disease in "yellow" mice fed the high-fat diet through life.

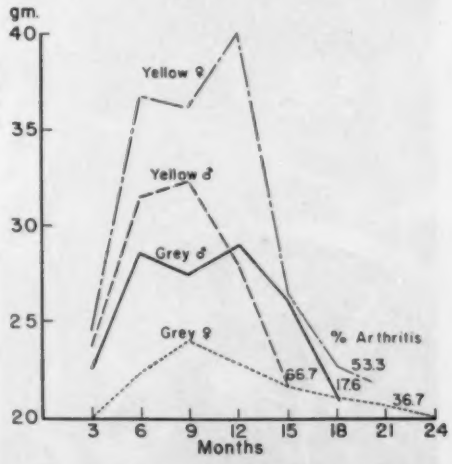


Chart 3.—Mean weight and incidence of degenerative joint disease in "yellow" mice fed the high-carbohydrate diet through life.

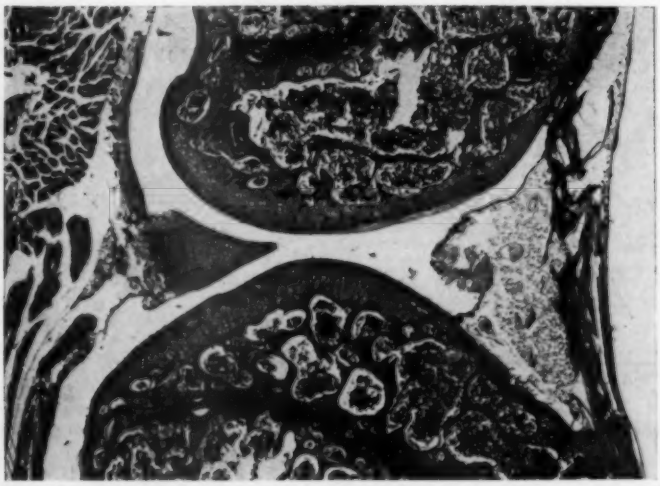
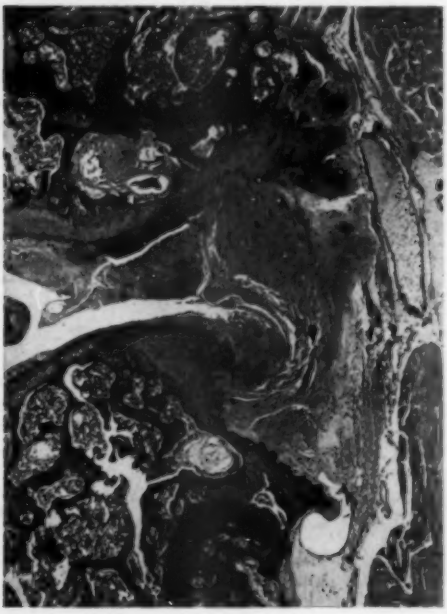


Fig. 1.—Unchanged knee joint. Articular surfaces show regular configuration. The femur is seen in the upper, the tibia in the lower part of the picture, the meniscus at the left. × 35.

addition, retarded epiphyseal development and osteosclerosis were observed.

3. *Articular Findings.*—The microscopic manifestations of articular aging and of degenerative joint disease have been fully described elsewhere.[3] Osteoarthritis as observed in mice of various strains may be either hypertrophic or ulcerative in type. Figures 1, 2, and 3 demonstrate an unchanged joint and two osteoarthritic joints.

Fig. 2.—Hypertrophic type of degenerative joint disease. Diffuse hyperplasia and hypertrophy of the articular cartilage with marginal osseous outgrowth, particularly at the tibia (top), thickening and degeneration of joint capsule and ligament, and cyst formation in the epiphyses of tibia and femur. Reduced slightly from mag. × 35.



Figures 2 and 3 illustrate changes classified as advanced. However, as reported and illustrated repeatedly, in many instances a variety of less severe articular lesions are found. These consist of varying degrees of hyperplasia and hypertrophy and regressive changes in the cartilage with or without superficial erosion. Ligaments, synovialis, and occasionally the capsule may show early involvement, and fibrosis and cyst formation in the epiphysis may be seen without erosion of the articular surface.[3]

The incidences of the lesions in the various experimental and control groups are given in Table 2.

A. In Mice Fed the Stock Diet: Of the gray-coated males, 16.7% had joint disease at the mean age of 17.5 months. Yellow-coated males of similar age showed a 36.4% incidence, indicating that the yellow-coated males were more susceptible to the joint disease than the gray-coated males.

Of the gray-coated females, 44.4% had articular lesions at the mean age of 20.3

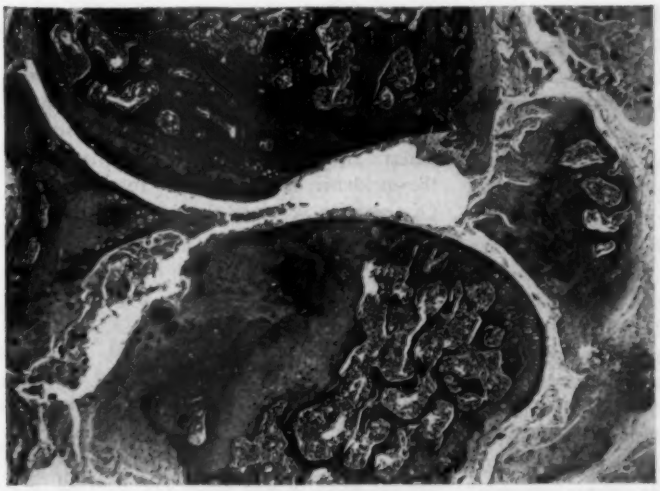


Fig. 3.—Ulcerative type of degenerative joint disease. Diffuse hyperplasia and hypertrophy of the remaining articular cartilage of the tibia (top), and focal hyperplasia and hypertrophy with the formation of "Brut" (incubator) capsules at the femur. There is a deep ulcer at the tibia, and loss of cartilage at the surface of the femur with baring of vascularized and eburnized bone. The menisci show, likewise, hyperplastic and regressive changes. × 35.

months. This represents a considerable increase over the 16.7% incidence seen in gray-coated males. This sex difference may constitute merely an age effect (the mean age at death of all gray-coated females exceeded that of all gray-coated males by three months), or it may be due to other injurious metabolic factors. Yellow-coated females showed a 42.3% incidence of joint disease at a mean age of 18.5 months. While the ultimate incidences thus seem to indicate a similar susceptibility of gray- and yellow-coated females, the articular lesions were severer in the former than in the latter. However, the yellow-coated females which had osteoarthritis were at death 1.8 months younger than gray-coated females with articular lesions, a difference in age that may account for the greater severity of these lesions in the gray-coated animals. There was no conspicuous sex difference in the incidence of the joint disease in the yellow-

TABLE 2.—*Incidences of Degenerative Joint Disease and Ages of Mice of the Various Groups*

Coat Color	Sex	Diet	No. of Mice	Mean Age at Death (Range: Mo.)	Osteoarthritis		
					No. of Mice	Per Cent of Total	Mean Age (Range: Mo.)
Gray	M	Stock	50	16.3 (9-22)	6	16.7	17.5 (12-22)
		High-fat	21	16.0 (12-21)	4	19.0	16.8 (13-20)
		High-carbohydrate	34	17.0 (9-19)	6	17.6	17.0 (16-18)
Yellow	M	Stock	33	15.8 (11-20)	12	36.4	17.3 (12-20)
		High-fat	22	13.3 (10-18)	9	40.9	15.2 (11-18)
		High-carbohydrate	24	16.6 (13-19)	16	66.7	16.8 (13-19)
Gray	F	Stock	27	19.3 (12-22)	12	44.4	20.3 (16-22)
		High-fat	28	17.4 (12-23)	15	46.5	18.4 (14-23)
		High-carbohydrate	30	19.9 (12-25)	11	36.7	22.4 (21-25)
Yellow	F	Stock	33	16.8 (10-22)	14	42.3	18.5 (12-22)
		High-fat	26	16.6 (11-19)	15	57.7	15.5 (11-19)
		High-carbohydrate	30	16.8 (15-20)	16	53.3	18.6 (15-20)

coated animals, although the females survived the males by three months.

B. In Mice Fed the High-Fat Diet: The effect of the diet varied with the group of animals tested.

In gray-coated males, the incidence of osteoarthritis and the age at which the disease was observed were practically unaffected by consumption of the enriched diet. In yellow-coated males, the over-all incidence of the articular lesions was likewise unchanged. However, the mean age of the yellow-coated males dying with the disease was 2.1 months lower than that of the stock-fed controls. Moreover, 18% of the animals fed the enriched diet had advanced articular lesions at the age of 15.2 months, while in mice fed the stock diet severe articular changes were not found before the age of 19 months. Thus, the high-fat diet accelerated the onset and intensified the progress of degenerative joint disease in yellow-coated males. This effect is even more impressive than would appear at first sight, because the mean life span of all yellow-coated males fed the high-fat diet was only 13.3 months. In other words, many of these animals did not live to an age at which age, as such, would materially contribute to the disease.

In gray-coated females, the enriched diet likewise accelerated the onset and increased the severity of the joint disease, although the ultimate incidence was similar to that seen in the stock-fed controls. The mean age at death of the former mice was 1.9 months lower than that of the latter. Moreover, at a mean age of 15.9 months 25% of the mice fed the enriched ration had advanced articular lesions, while none of the stock-fed controls were severely affected at this age. The joints of yellow-coated females proved to be highly susceptible to the injurious effect of the high-fat diet, which raised the over-all incidence to 57.7%. The mean age of mice that had developed articular lesions was three months lower than that of the stock-fed controls. The incidence of advanced lesions showed a slight increase from 27% in stock-fed controls to 38% in animals fed the enriched diet.

C. In Mice Fed the High-Carbohydrate Diet: The diet failed to exert any noteworthy effect in the joints of gray-coated males. In yellow-coated males, by contrast, the incidence of joint disease rose to 66.7%. Of the mice younger than 18 months, 44% had advanced articular changes, while none of such severity were seen in correspondingly old stock-fed controls. In the oldest age group of the mice fed this enriched ration all joint lesions were advanced, while of the correspondingly old stock-fed controls only one-half of the lesions had reached this stage.

Gray-coated females proved resistant to the influence of this diet. The over-all incidence of osteoarthritis in these mice was 36.7% as compared with 44.4% in the stock-fed controls, even though the mice which had developed joint disease were, on the average, 2.1 months older than the stock-fed controls. Furthermore, only 17% of the mice fed the enriched ration had advanced lesions, while 33% of the stock-fed controls were thus affected. This indicates slow progress of the joint disease in mice fed the high-carbohydrate diet. In yellow-coated females the enriched diet raised the incidence of osteoarthritis to 53.3% as compared with a 42.3% incidence found in stock-fed controls. This effect is not striking, but at the same time the incidence of severe articular changes rose from 21% to 47%.

COMPARISON OF THE EFFECTS OF THE HIGH-FAT AND HIGH-CARBOHYDRATE DIET

This comparison might be helpful in determining whether the effects of the high-fat ration are due specifically to the fat or to the high-calorie value of the diet.

Both rations were practically ineffective as far as the joints of gray-coated males are concerned. Since the life span of these animals was likewise unaltered by the rations, it seems that the metabolism of gray-coated males is capable of coping with unbalanced diets. In gray-coated females, the high-carbohydrate diet proved less injurious than

the high-fat diet. The mean life span was not shortened by the high-carbohydrate diet, and the joint lesions were less frequent and less severe than in mice fed the fat-enriched ration.

Yellow-coated males responded unfavorably to either diet. The high-fat ration accelerated the onset and progress of the articular lesions, while at the same time shortening the life span of these mice. The high-carbohydrate diet permitted the animals to live to a considerably higher mean age than the high-fat diet. The increased incidence of joint disease observed in mice fed the high-carbohydrate ration may thus be partly an effect of age and only partly due to some injurious effect of the high-carbohydrate ration itself. Such injurious action may be related to the increased caloric intake or to the ensuing obesity or to a more or less specific metabolic effect of the carbohydrates consumed. In yellow-coated females, feeding of either of the enriched diets increased the over-all incidence of osteoarthritis to about the same extent. However, the high-carbohydrate diet did not accelerate the onset of the articular lesions and failed to shorten the life span as did the fat-enriched ration. These findings indicate a more harmful effect of the high-fat diet than of the high-carbohydrate diet. These observations are in agreement with previous findings in growing mice fed isocaloric rations high in fat or carbohydrate, respectively. In these experiments it was shown that the injurious effect of the high-fat diet was due partly to the high-caloric value of the ration but in part also to the fat specifically.[6]

CORRELATION OF BODY WEIGHT AND DEGENERATIVE JOINT DISEASE

In stock-fed animals, there was no correlation between body weight and the incidence of spontaneous joint disease. Gray-coated males weighed more but showed fewer articular lesions than gray-coated females. Yellow-coated males were heavier than yellow-coated females. Nevertheless, the incidence of osteoarthritis was about the same in both groups of animals.

Consumption of the enriched rations failed to cause obesity in gray-coated males or to change the incidence of osteoarthritis. Gray-coated females developed slight overweight under the influence of the high-fat or high-carbohydrate diet, respectively. The incidence of joint disease was not increased; however, under the influence of the high-fat diet, the onset of osteoarthritis was accelerated, and the severity of the joint lesions increased.

Yellow-coated males became obese following consumption of either of the enriched rations. Obesity was present from 5 months of age on and lasted through the 10th month; it reached a peak of about 25% above normal in the mice fed the high-fat ration and was slightly less marked under the influence of the high-carbohydrate diet. In both groups of animals, the course of the joint disease was accentuated, the onset was accelerated, and the severity of the lesions intensified. The high incidence of articular lesions in males fed the high-carbohydrate diet may be related to the comparatively high age that these animals reached as compared with that of males fed the stock or high-fat rations. Whatever the reason, there seems to exist in the yellow-coated males a positive correlation between the presence of obesity and the intensification of osteoarthritis.

The findings in yellow-coated females were basically similar to those seen in yellow-coated males. However, in females obesity reached a peak of 60% to 70% above normal, and it was present from about 3 months of age to the age of 14 months and more. Marked individual variations in weight were associated with a marked increase in the incidence of osteoarthritis and with an accelerated onset of the disease. Thus, statistically a positive correlation between obesity and joint disease was present in this group of mice also. However, obesity was noted not only in mice that had osteoarthritis but also in animals with unaltered joints or with joints that showed only minor age changes.

Table 3 shows the mean maximum weights in yellow-coated females grouped according to the articular findings.

Furthermore, if the mice were grouped according to the degree of overweight and the incidences of osteoarthritis were determined for these groups, the correlation between these two conditions was found to be more restricted than would appear from the statistical correlation. The data on which this conclusion is based are given in Table 4.

As seen from Table 4, about one-half of the mice reaching a weight of over 40 gm. on either the high-fat or the high-carbohydrate

TABLE 3.—*Mean Maximum Weights in Yellow-Coated Females According to the Articular Findings*

Diet	Maximum Mean Weights, in Gm., of Mice Showing		
	Unchanged Joints	Articular Age Changes	Osteoarthritis
High-fat	45.5	47.6	47.7
High-carbohydrate	....	40.2	40.7

TABLE 4.—*Correlation Between Various Degrees of Obesity and Degenerative Joint Disease in Yellow-Coated Females*

Diet	Maximum Wt., Gm.	Mean Duration of Overweight, Mo.	Osteoarthritis	
			Per Cent	Mean Age, Mo.
Stock	20	..	42	18
High-carbohydrate	41-50	12	55	19
High-fat	41-50	11	42	17
	51+	12	71	15

ration developed joint disease. This incidence varies only slightly from the 42% incidence observed in nonobese stock-fed controls. Only in cases of extreme obesity—that is, in mice reaching a weight of more than 50 gm. and remaining obese for about 12 months—was the incidence of osteoarthritis markedly increased. Under these conditions, almost three-fourths of all mice were affected and all articular lesions were advanced in degree. These findings indicate that, while slight or moderate degrees of obesity had no appreciable effect on the articular tissues, excessive obesity may have played a contributory role in the development of osteoarthritis.

COMMENT

Mice of strain YBR/Wi developed osteoarthritis, as do mice of other strains.‡ No correlation could be established between the occurrence of joint disease and other visceral lesions, such as ophthalmitis, aortitis, pyelonephritis, or amyloidosis, commonly found in these animals. In contrast to C57BL females, untreated gray-coated females of strain YBR/Wi were more severely and more frequently affected with osteoarthritis than males of the same strain. This finding may be related to the fact that, unlike C57BL females, YBR/Wi females outlived the males.[8] However, the marked endometrial hyperplasia found in aging YBR/Wi mice points to the presence of some endocrine disorder. Since the structure of the cartilage may be influenced by a number of hormones, the endocrine imbalance causing endometrial hyperplasia may play a role in the development of the articular lesions observed. Association of endometrial hyperplasia with disturbances in progesterone or estrogen activity is common in man,§ and has also been found in hybrid mice.[9] In our mice, the mammary glands were not stimulated, and maturation of the epiphyseal cartilage was delayed.[10] Moreover, as will be reported elsewhere, administration of estrogenic hormone did not further increase the hyperplasia of the endometrium. It is, therefore, unlikely that excessive amounts of estrogen were produced by these animals. The marked luteinization of the ovaries noted in our mice, as well as by previous investigators,[11] may well be related to the endometrial hyperplasia. On the other hand, excessive amounts of progesterone may counteract the condensation of cartilage caused by endogenous estrogen. Moreover, there are also indications that YBR/Wi mice are relatively hypothyroid.[10] The retarded epiphyseal development and the osteosclerosis of the long bones closely resembled findings obtained in mice of strain DBA made thyroid-deficient by injections of I^{131}. The coincidence of these

‡ References 3 and 4.

§ References 7 and 8.

changes in YBR/Wi mice with a high incidence of degenerative joint disease, as was also present in radiothyroidectomized DBA mice, thus represents the counterpart of conditions observed in absolutely or relatively hyperthyroid mice, namely, accelerated epiphyseal development and ageing and a low incidence of joint disease. In YBR/Wi mice we may, therefore, have to deal with a pattern of hormone secretion that favors the development of articular lesions.

The present observations may be of interest in regard to the role of osteoporosis in the pathogenesis of osteoarthritis.‖ YBR/Wi mice have no tendency to develop osteoporosis. On the contrary, they tend to develop marked osteosclerosis with advancing age.[10] However, there was no indication that females with sclerotic bones are less prone to acquire joint disease than mice with nonsclerotic bones.

The body weight of untreated YBR/Wi mice was apparently not related to the development of osteoarthritis. Moderate degrees of obesity did not influence the course of the disease to any appreciable degree. Similar conditions prevailed in males of strain C57BL fed a high-fat diet; in these animals, overweight of about 25% did not exert a definite influence on the articular lesions.[3] Moderate obesity and an increased tendency to osteoarthritis may thus coexist, but this coexistence does not imply a cause-and-effect relationship between the two. Excessive obesity, however, present over an extended period of time, as seen in our yellow-coated females, may play a contributory role in the pathogenesis of osteoarthritis.

The response to enriched diets, in particular to the high-fat ration, varied with sex and coat color. Gray-coated males appeared resistant, and their reaction therefore resembled that of DBA males, which developed neither obesity nor marked articular lesions if fed a high-fat ration.[4] In all other groups, but especially in yellow-coated animals, the high-fat diet exerted an unfavorable effect on the joint disease. Yellow-coated animals fed a high-fat ration became obese and had a considerable incidence of joint disease in spite of their shortened life span. This difference between gray- and yellow-coated animals may be interpreted in two ways: the Y′ gene may be responsible for traits other than coat color and the tendency to obesity; or, the tendency to obesity and osteoarthritis may have some common etiologic background that is transmitted by the Y′ gene. This common etiologic factor may be related to the avidity of bearers of the Y′ gene for enriched diets, or to the metabolism of the increased food consumed.

The joints of yellow-coated males proved highly susceptible to the high-carbohydrate diet. Obesity and the comparative longlivedness of these mice would in all likelihood not be wholly responsible for this reaction. The high incidence of hypertrophic pancreatic islets in these mice might represent a response to consumption of the high-carbohydrate diet. This hypertrophy might release pathological endocrine or neuroendocrine mechanisms, which may ultimately involve the articular tissues. That the hypertrophy of the pancreatic islets as such did not account for the high incidence of osteoarthritis is indicated by the moderately frequent occurrence of such hypertrophic islets in gray-coated males, which are comparatively resistant to degenerative joint disease.

The changes in the pancreatic islets are of particular interest in view of the high blood-sugar levels observed in these mice.[5] Conceivably, these changes may result from hypophyseal or hypothalamic disturbances, which in turn would provide a link to the hyperphagia and obesity noted in yellow-coated mice fed enriched diets.

SUMMARY

Mice of the yellow strain YBR/Wi developed spontaneous degenerative joint disease, an analogue of the human disease, as do mice of other strains. In yellow-coated males and females as well as in gray-coated females of this strain a high incidence of the articular lesions was observed, while gray-

‖ References 12 to 15.

coated males were less severely affected. A high-fat diet promoted the course of the disease in all groups except gray-coated males. A high-carbohydrate diet exerted injurious effects on the joints only in yellow-coated mice. Moderate obesity had no adverse influence on the evolution of osteoarthritis; excessive obesity, however, may have played a contributory role in the development of the joint disease. There were indications that neuroendocrine or endocrine imbalances exist in mice of this strain. The possible relationship of these disturbances to the articular lesions is discussed.

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Infantile Lobar Emphysema

An Etiological Concept

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In recent years a newly recognized disease entity has been described* and reported in the pediatric literature. This has been referred to as congenital emphysema, hypertrophic emphysema of infants, or infantile lobar emphysema. It is a rare condition characterized clinically by the sudden onset of dyspnea and cyanosis in infants. Death usually occurs as a result of rapid progression of respiratory embarrassment. A single lobe of the lungs, usually an upper lobe, shows severe hypertrophic emphysema, whereas the remaining lung tissue is atelectatic by virtue of compression. Surgical removal of the affected lobe has resulted in the apparent cure of a number of these patients.*

In the majority of cases described, pathologic studies have failed to reveal the cause of the emphysema. In other cases, various obstructive bronchial lesions have been reported, although the authors often imply that these seemed insufficient to produce such an acute fulminant change. To refute the concept that bronchial abnormalities may play a contributing role in the production of this emphysema would be erroneous, although the absence of such lesions in most of the cases suggests the possibility of additional pathologic alterations. Mayer and Rappaport † have stressed the concept that emphysema may not always be the result of partial bronchial or bronchiolar obstruction alone. According to these authors, predisposing alterations of the pulmonary parenchyma must be present before primary emphysema can occur under any circumstances. In this light, a histologic study was undertaken to determine if any consistent changes are present in the pulmonary parenchyma which might reflect on the etiology.

MATERIALS AND METHODS

The records of the Children's Memorial Hospital (1938-1954) disclosed seven cases ‡ meeting the following criteria:

1. Onset of respiratory distress in neonatal period or infancy
2. Surgical or autopsy evidence of localized pulmonary emphysema which was primary and severer than other changes in the lungs
3. The presence of no other disease affecting the cardiac or respiratory systems, such as congenital heart disease, pulmonary infection, etc.

Eight other cases were chosen for control purposes. Two cases of emphysema in infants of other types were selected. One case represented a 6-week-old infant with persistent atelectasis of the right lung and compensatory emphysema of the left lung; the other, a 3-month-old infant with severe emphysema secondary to acute bronchiolitis. Six cases with relatively normal, nonemphysematous lungs were chosen in which the patients had died from other than cardiorespiratory disease, and these cases included a wide age range. Three of these cases were newborns dying of erythroblastosis fetalis at one day of age. A hydrocephalic infant dying at 1 month of age, a 12-month-old infant dying of cerebral hemorrhage, and a 14-month-old infant dying of meningitis were also included.

The emphysematous lung tissue from each of the cases of infantile lobar emphysema and the lung tissue from the controls had been previously fixed in

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* References 7-9, 11, 13, and 14.

† References 10 and 12.

‡ Three of the cases selected were reported previously by Fischer, Potts, and Holinger in 1952.[11] These are Cases 2, 4, and 6.

Zenker's solution and embedded in paraffin. The tissue was reembedded in paraffin, and new sections 5μ thick were cut. These sections were stained simultaneously with hematoxylin and eosin and Mallory's aniline blue.[15] Slides were prepared in the usual manner and reevaluated microscopically.

REPORT OF CASES

The following represent summations of the clinical and pathologic findings as recorded in the patients' hospital charts.

CASE 1.—A white boy was well until the 16th day of life when there was a rapid onset of dyspnea and cyanosis. On physical examination there was marked hyperresonance over the right hemithorax. X-ray examination revealed a severe emphysema of the right upper lobe with mediastinal shift to the left. Surgery was performed shortly after admission. A right upper lobectomy was performed. The patient did well postoperatively. Six days after surgery x-rays revealed normal lung expansion.

The specimen consisted of the upper lobe of the right lung. Its pleural surfaces were yellowish-orange. Focal areas of subcrepitance were palpable in the superior portions of the lobe, but in general there was marked hypercrepitance throughout. On section, frothy pink material exuded from the cut surface. Numerous small cystic spaces were present. No bronchial abnormalities were noted. Microscopically, the alveolar spaces were greatly enlarged and circular. The bronchioles were dilated. The alveolar walls were thickened. Normal-appearing cartilage was present in the bronchial walls.

CASE 2.—A 4-month-old white boy was in good health until the 6th week of life, when he developed dyspnea, cyanosis, and cough. The patient was admitted to the hospital, and physical examination revealed a marked increase in resonance over the right hemithorax. X-ray examination disclosed emphysema of the right middle lobe. The patient was taken to surgery, where a markedly emphysematous right middle lobe was seen to herniate through a defect in the anterior mediastinum. No other abnormalities could be found. The abnormal lobe was removed, and the patient made an uneventful recovery. X-rays on the eighth postoperative day revealed normal lung expansion.

The specimen consisted of the middle lobe of the right lung. There was a marked increase in crepitancy throughout. The visceral pleura was smooth and glistening, and through it, the lung substance appeared pale reddish-gray. Emphysematous blebs were present, which measured up to 4 mm. in diameter. Cut surfaces revealed a pale reddish-gray parenchyma from which frothy, pink fluid could be expressed. No bronchial abnormalities were noted. Microscopically, there was a marked degree of emphysema. The alveoli were distended and sometimes ruptured. Their walls appeared thickened, and a small amount of precipitated eosinophilic material was present in the lumina. The bronchioles and larger bronchi appeared normal. There was no evidence of abnormalities of the cartilage associated with these structures.

CASE 3.—A 7-week-old white boy was admitted to this hospital because of choking and crying spells of one week's duration. Physical examination on admission was not remarkable. X-ray examination revealed a marked degree of emphysema involving most of the left lung. The mediastinum was shifted to the right. Bronchoscopy revealed right tracheal deviation, and the right main and upper lobe bronchi were distorted and kinked but not appreciably obstructed. The left main bronchus appeared to be obstructed by compression. Only a 3.5 mm. bronchoscope could be passed into this bronchus. At surgery, a marked degree of emphysema of the left upper lobe was present, and this lobe was removed. The patient made an uneventful recovery. Two months after surgery, x-ray showed a homogeneous density obscuring the upper third of the left lung, probably representing thickened pleura.

The specimen consisted of the upper lobe of the left lung. The superior portion was hypercrepitant and pale reddish-gray. The inferior portion was subcrepitant and collapsed. There was a stenotic bronchus entering the superior portion of the lobe. The stenosis was associated with marked thickening of the bronchial wall in that area. Microscopically, the area of stenosis was the seat of round-cell exudate and fibrosis. The bronchial cartilage did not appear remarkable. There was a marked degree of pulmonary emphysema with focal atelectasis.

CASE 4.—A 3-month-old white boy began to vomit at 3 weeks of age. There was a moderate degree of dyspnea. Two weeks later he was admitted to this hospital, where physical examination revealed hyperresonance of the left chest. The heart was shifted to the right. X-rays showed the left lung to be unusually radiolucent, and the mediastinum was shifted to the right. A bronchogram failed to reveal evidence of bronchial abnormality. At bronchoscopy, the trachea was deviated to the right. The left lower lobe bronchus was slightly narrowed. At surgery, the left upper lobe was found to be extremely emphysematous. A persistent ductus arteriosus was seen to extend over the left main bronchus. This structure was divided, and the left upper lobe removed. The patient made an uneventful recovery. Ten days after surgery, x-rays revealed normal lung expansion.

The specimen consisted of the upper lobe of the left lung. There was a marked increase in crepitancy. Large bullae, measuring 15×5 mm., were present on the surface. The pleural surfaces were smooth and glistening, and the tan-gray color of the parenchyma could be seen through it. Cut surfaces re-

vealed a spongy, yellowish-gray to pink parenchyma. Large air spaces measuring up to 7 mm. in diameter were identified. No bronchial abnormalities were identified. Microscopically, there was marked dilatation of alveoli with focal rupture of their walls. Some of these air spaces contained precipitated eosinophilic material. The bronchi and bronchioles did not appear unusual.

CASE 5.—A 2-month-old white boy was admitted to the hospital with a history of "collapsed lung since birth." Physical examination revealed hyperresonance of the right hemithorax. X-ray examination revealed marked emphysema of the right upper lobe. Bronchoscopy was not performed. At surgery, a markedly emphysematous right upper lobe was found, which was removed. The patient made an uneventful recovery. X-rays taken six months after surgery were not remarkable.

The specimen consisted of the upper lobe of the right lung. The pleural surfaces were smooth and glistening. There was no evidence of blebs or bullae. Cut surfaces revealed marked hypercrepitance and a honeycombed, pale reddish-gray appearance. The bronchi were not remarkable. Microscopically, the alveoli were markedly dilated, and focal rupture of the walls produced large cyst-like spaces. In some areas there appeared to be thickening of the alveolar walls. The bronchi and bronchioles were not remarkable.

CASE 6.—A 2-month-old white girl was admitted to this hospital because of the sudden onset of wheezing and cyanosis. At one month of age, two short episodes of dyspnea and cyanosis had been noted. Physical examination revealed the patient to be critically ill. The right hemithorax was hyperresonant. X-rays showed a marked degree of emphysema of the right middle lobe. Bronchoscopy was not performed. At surgery, a markedly emphysematous right middle lobe was removed. No other unusual features were noted at that time. The patient made an uneventful recovery.

The specimen consisted of the middle lobe of the right lung, which was roughly triangular and hypercrepitant. The pleural surfaces were smooth and glistening. On section, the parenchyma was honeycombed and pale reddish-gray throughout. Pressure caused the emanation of frothy, pink fluid. Microscopically, there were markedly distended alveoli with slightly thickened walls. The air spaces contained a moderate amount of precipitate eosinophilic material. The bronchi studied had a diminished amount of cartilage, and the mucosa showed frequent infoldings.

CASE 7.—A white girl entered this hospital at 6 weeks of age, with a history of wheezing, dyspnea, and cyanosis since the first week of life. Physical examination on admission revealed a dyspneic infant with marked suprasternal retractions. The heart was shifted to the right, and the right hemithorax was hyperresonant. Fluoroscopy showed the left lung to be markedly radiolucent, but a bronchogram failed to reveal evidence of obstruction. At bronchoscopy the left main bronchus was almost completely occluded. Landmarks were very distorted, so that orientation was difficult. Breathing became more labored after this procedure. On the 16th hospital day the patient died.

At autopsy the major findings consisted of marked emphysema of the left lung, moderate atelectasis of the right lung, and mediastinal shift to the right. The left lung was uniformly hypercrepitant, being pale reddish-gray with prominent lobular markings on the pleural surface. There was no evidence of extrinsic compression of the bronchi. In the distal and middle third of the left main bronchus, no cartilaginous rings were identified grossly, although these were visible in the proximal one-third of this structure. Microscopically, sections of the left lung revealed marked distention of alveoli with rupture of the walls. Serial sections through the right main bronchus showed seven or eight well-formed cartilaginous rings, but only three to four in the left main bronchus. The etiology of the emphysema was thus attributed to hypoplasia of the cartilaginous rings in the left main bronchus.

RESULTS

The hematoxylin and eosin sections in all cases of infantile lobar emphysema revealed fairly uniform findings corresponding closely in most instances with the changes originally described. The pleurae were thin and not unusual. The small arteries and arterioles showed no evidence of hypertrophic change. The bronchi and bronchioles were not significantly altered in the sections studied. There was a moderate to marked degree of passive hyperemia with occasional intra-alveolar hemorrhages. The alveoli were moderately to markedly distended, and there was focal rupture of the septa, producing larger cyst-like air spaces. Focal precipitates of eosinophilic proteinoid material were present in the air spaces, but there was no evidence of hyaline-membrane formation or inflammation. Patchy foci of atelectasis were interspersed between distended alveoli. In most areas, the supporting stroma of the alveolar walls appeared thickened. This thickening varied somewhat from case to case and from site to site in the same lung. Within the stroma, many elongated cell forms, some with spindle-shaped nuclei, were embedded

in a matrix of delicate, slightly refractile fibrils. In many instances the inner surfaces of the alveoli were also lined by elongated, flattened cells, which also appeared in association with refractile fibrils. This tissue was thought to represent immature collagenous connective tissue. There was bright blue staining of these cells and fibrils with Mallory's aniline blue, which tended to confirm the impression. The changes described were present in all the cases of infantile lobar emphysema. This contrasted sharply with the control cases, where there was a paucity or complete absence of blue-staining tissue, except in relation to blood vessels or bronchi (see Table 1). It was thought that the situation described may possibly represent an abnormal deposition of collagenous connective tissue in the alveolar supporting stroma and lining.

TABLE 1.—*Histologic Evaluation of Cases Studied and Controls*

Case	Edema	Focal Atelectasis	Hyaline Membrane	Alveolar Fibrosis	Emphysema
Cases of infantile lobar emphysema					
1	1+	3+	0	4+	4+
2	2+	0	1+	4+	4+
3	0	1+	0	4+	3+
4	1+	1+	0	4+	4+
5	2+	3+	0	2+	4+
6	1+	1+	0	2+	3+
7	2+	0	0	3+	4+
Control Group I.—Emphysema of other types					
1	1+	0	0	0	4+
2	1+	2+	0	0	4+
Control Group II.—Normal lungs					
EBF 1*	0	2+	0	0	0
EBF 2*	1+	2+	0	0	0
EBF 3*	1+	2+	0	0	0
X†	2+	3+	0	0	0
Y‡	0	1+	0	0	0
Z§	1+	1+	0	0	0

* EBF, erythroblastosis fetalis: age 1 day.
† X, hydrocephalic: age 1 month.
‡ Y, cerebral hemorrhage: age 12 months.
§ Z, meningitis: age 14 months.

In the seven cases studied, no correlation of the severity of changes could be drawn with the age of onset, location of the lesion, or the presence or absence of bronchial abnormality. In three of the cases, there was no evidence of bronchial abnormality. Two had hypoplastic cartilaginous rings, and one revealed an inflammatory stenosis of a bronchus. In another case, a ductus arteriosus was seen to slightly compress the bronchus.

COMMENT

Emphysema in infants was a confused and unexplored subject as late as 1930. Kountz and Alexander [2] recognized the existence of emphysema in infants but made only brief mention of it. It was believed that localized emphysema occurring in the lungs of an infant was almost invariably associated with, or a part of, congenital cystic disease. Emphysema without cystic disease was considered a rarity, although very few cases of either condition were recorded in the literature.§ A number of isolated cases of localized emphysema without cystic disease began to be reported in the literature,‖ followed by several series of cases,¶ so that at the present time over 30 cases are on record. An analysis of 23 cases from the literature plus the 7 reported here show that the disease has occurred exclusively in the Caucasian race, and more frequently in boys. The lesions were usually confined to a single upper lobe, most frequently the left upper lobe.

Numerous etiologic explanations for this condition have been advanced, but no one has been universally applicable. The causative mechanisms suggested by the various authors fall into several groups:

A. Bronchial lesions.
   1. Check-valve obstruction. Cases have been described in which the emphysema was attributed to check valves formed by redundant infoldings of bronchial mucosa.[7]
   2. Abnormalities of bronchial cartilage. Marked flaccidity of the bronchial walls produced by abnormal cartilaginous rings has been observed. This is believed to result in obstructive collapse of the bronchus during expiration, thereby producing emphysema.
   3. Bronchial stenosis, cysts, and mucous plugs have been similarly indicted.#

B. Bronchial compression. Compression of a bronchus by aberrant blood vessels or the ductus arteriosus has been reported. These structures were thought to produce emphysema by exerting occlusive pressure on the bronchus.*

§ References 1 and 3.
‖ References 3, 6, and 8.
¶ References 7, 9, 11, 13, and 14.
# References 11 and 13.
* References 7 and 11.

C. Lesions of the pulmonary parenchyma.

1. Earlier concepts held that there was a congenital diminution of elastic tissue in the alveolar walls.[2] This is no longer considered tenable, since elastic tissue is meager in normal infants' lungs.
2. The occurrence of this disease has been reported in infants receiving overly vigorous resuscitation at birth. These cases are relatively few.†
3. It was noted that the lesion tended to occur in the upper lobes. This was believed to be due to the diminished expiratory forces acting on the upper lobes. In these areas, expiration is thought to be more dependent on the contractile properties of the pulmonary parenchyma.[11]

In the 23 cases reviewed in the literature, 15 showed no evidence of bronchial abnormality. Five of these received vigorous mechanical resuscitation at birth. Hypoplastic cartilaginous bronchial rings or chondromalacia were reported in four cases, and bronchostenosis, in three. Extrinsic bronchial compression was present in two cases. Redundant mucosal infolding was identified in two cases. If an etiologic common denominator is present, it is not apparent from this survey of the literature (see Table 2).

It would seem possible that the alveolar fibrosis observed in our seven cases may represent an important etiological factor. This does not imply that other factors producing partial bronchial obstruction are to be disregarded. It would seem, however, that the fulminant emphysema developed by these patients may be difficult to explain on the basis of bronchial alteration alone, particularly when the majority of cases display no such alteration, or only minor ones. Such a concept is in keeping with the thinking of Mayer and Rappaport,‡ who speculate

† References 7, 9, and 13.

‡ References 10 and 12.

TABLE 2.—*Analysis of Cases Reported in the Literature Plus This Series*

Author, Year, Case No.	Age at Onset of Symptoms	Sex	Site of Lesion	Bronchial Lesion	Miscellany
Nelson (1932)	4 mo.	M	LUL	Chondromalacia Hypoplastic cartilage	Patient died and was necropsied
Overstreet (1939)	1 mo.	M	LUL	Hypoplastic cartilage Stenotic, thick bronchus	Patient died and was necropsied
Leahy and Butsch (1949)	Birth	M	LUL	None	Mechanical resuscitation at birth
Robertson and James (1951)					
1	10 days	M	RUL	Mucosal folds	Died at 3 mo.
2	2 wk.	M	RUL	None	Operated and recovered
3	5 mo.	M	RUL	Anomalous vein around bronchus	Died at 9 mo.
4	2 wk.	M	LUL	Mucosal folds	Operated and recovered
5	1 mo.	F	RML	None	Operated and recovered
Williams (1952)	Birth	M	RML	None	Operated and recovered
Shaw (1952)					
1	2 wk.	M	LUL	None	Operated and recovered
2	2 wk.	F	RML	Flaccid bronchus	Operated and recovered
Ehrenhaft and Taber (1953)					
1	Birth	M	LUL	Small bronchus	Operated and recovered
2	Birth	F	LUL	None	Died 3 mo. after surgery with bilateral emphysema
3	Birth	F	RML	Slit-like bronchus	Operated and recovered
4	1 wk.	F	RML	None	Operated and recovered
5	Birth	F	Generalized	None	Died 24 hr.*
6	Birth	M	Generalized	None	Died 24 hr.*
7	Birth	M	Generalized	None	Died 4 mo.*
8	Birth	M	Generalized	None	Died 1 yr.*
Sloan (1953)					
1	3 wk.	M	RML	None	Operated and recovered; emphysema on follow-up x-rays
2	3 days	M	LUL	None	Operated and recovered; emphysema on follow-up x-rays
3	7 wk.	F	LUL	None	Operated and recovered
4	4 wk.	M	RML	None	Operated and recovered
This series (1954)					
1	16 days	M	RUL	None	Operated and recovered
2	6 wk.	M	RML	None	Operated and recovered
3	7 wk.	M	LUL	Inflammatory stenosis	Operated and recovered
4	3 mo.	M	LUL	Ductus arteriosus	Operated and recovered
5	Birth	M	RUL	None	Operated and recovered
6	1 mo.	F	RML	Hypoplastic cartilage	Operated and recovered
7	1 wk.	F	L. lung	Hypoplastic cartilage	Died and autopsied

* All cases had vigorous mechanical resuscitation at birth.

on alterations of the pulmonary parenchyma which would predispose to the development of emphysema. These authors postulate that some of these alterations might be congenital or developmental in nature.

The functional effect of such alveolar fibrosis could manifest itself in several ways. During inspiration, the impact of rhythmic dilatation would tend to stretch the fibrotic alveoli. Expiration, depending largely upon the inherent contractile properties of the pulmonary parenchyma, would tend to be hampered by virtue of the increased rigidity of alveolar walls. It is apparent that this oft-repeated sequence of events could eventuate in emphysema.

The very young age of the patients and rapid course of the disease would seem to indicate that the fibrosis does not develop secondary to the emphysema. It would be more logical to assume that the fibrosis is congenital, with its effects becoming manifest shortly after birth. Such a "fibrous dysplasia" does not seem impossible from histogenetic considerations.[5]

Although there may be a relationship between this condition and congenital alveolar dysplasia described by MacMahon,[4] certain striking differences are present. In congenital alveolar dysplasia, MacMahon showed that the alveolar thickening was due to a mesenchymoid tissue devoid of collagen fibers, analogous to fetal lung. This observation allowed him to postulate retarded alveolar development. Emphysema was not part of the picture, and death was usually due to anoxia shortly after birth. In infantile lobar emphysema, there is no suggestion of fetal appearance, and an abnormal amount of collagenous connective tissue appears to be present.

On the other hand, if an infant with congenital alveolar dysplasia were to survive, it is conceivable that rapid differentiation and maturation of the mesenchymal elements might produce a picture similar to infantile lobar emphysema. Such a relationship might merit investigation.

SUMMARY

Seven cases of infantile lobar emphysema are presented and the emphysematous lung tissue described histologically. Increased amounts of collagenous connective tissue appear to be present in the alveolar walls in all cases.

Etiologic speculations based on pathologic, clinical, and physiologic considerations are presented.

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Carcinogenesis and Altered Host Reactions in Parabiotic Rats

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In experiments reported by Bielschowsky and Hall,[1] female parabiotic rat pairs were hemicastrated and the intact partners were fed a carcinogen. The combined endocrine imbalance and chemical carcinogen were effective in inducing various neoplasms, particularly of ovaries and breast. To our knowledge this ingenious technique has not been imitated, or the results confirmed.

This report concerns 69 parabiotic rat pairs subjected to procedures that damaged endocrine glands and thereafter fed the chemical carcinogen 2-acetylaminofluorene (AAF).* Confirmation of the original work was achieved with use of 23 female hemicastrated parabiotic rat pairs. Attention was particularly directed to the sequential changes that occurred in endocrine glands, target organs, and other major tissues microscopically, making use for this purpose of pairs that died or were killed during the latent period of carcinogenesis.

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* References 2 and 3.

Because radiothyroidectomy in mice stimulated the formation of amphophile pituitary adenomas,[4] with secondary mammary and uterine stimulation, possibly not mediated through the ovary, 18 hemiradiothyroidectomized rat pairs were also carcinogen-treated. These animals did not develop cancers, as had been anticipated, but instead proved relatively unresponsive to the AAF carcinogen. Studies of their sequential tissue alterations provided a contrast to the hemicastrated series and, indirectly, were of interest in relation to Bielschowsky's experimental thyroid cancer induction.†

In some human cancers analogous mechanisms seem sometimes to have been involved, as judged by the tissue changes at autopsy, so that these experiments have possible clinicopathologic correlations.

MATERIALS AND METHODS

Slonaker rats, usually littermates, were joined in parabiosis by the Bunster-Meyer celioanastomosis technique at 4 to 6 weeks of age. Female pairs were usually further treated by castration of the right-hand parabiont, and male pairs were mostly joined after radiothyroidectomy of one partner.

Female Hemicastrate Series.—Parabiotic pairs were prepared, and surgical castration of the right-hand partners was performed at the same operation or two to eight days later. After an 11- to 19-day interval, the carcinogen 2-acetylaminofluorene (AAF), 5 mg. in 0.5 ml. of peanut oil, was administered by stomach tube to the intact left-hand partners of 13 pairs three times per week. Treatment was continued for 14 to 18 weeks, with total doses of 215 to 275 mg. of AAF.

Radiothyroidectomy Series.—Parabiont pairs were prepared with partners differing about 10 gm. in weight. The heavier rat was given 1.5 mc. of I^{131} by intraperitoneal injection 8 to 20 days before

† References 5 and 6.

surgical parabiosis. Radiothyroidectomized rats were made the right-hand partners. Surviving pairs were divided into three experimental groups for further treatment, aside from controls.

Group I (Propylthiouracil): Beginning two to four months after parabiosis, 40 mg. of propylthiouracil in 1 ml. of 5% acacia solution was administered via stomach tube three times per week to seven intact parabiotic partners. Treatment was continued until the animals were killed 146 to 633 days later. The dose was sometimes decreased when animals appeared ill.

Group II (AAF): Five months after parabiosis, 5 mg. of AAF in 0.5 ml. of peanut oil was given by stomach tube to four intact parabiont partners three times per week. Treatment continued 10 to 16 weeks, with total doses of 170 to 240 mg. of AAF.

Group III (AAF and Propylthiouracil): Using the same method as in Group II, AAF was given over a five- to seven-week period, total doses being 90 to 105 mg. Thereafter propylthiouracil was administered as in Group I until death of the four pairs 30 to 450 days after AAF treatment ceased, or 127 to 636 days after the experiment began.

Controls.—In four hemicastrate female pairs AAF was administered to the right-hand castrated parabiont. Peanut oil alone was given as described above to the left-hand female partners of two other pairs. Following radiothyroidectomy, three male pairs were maintained without further therapy for 161 to 645 days. Two male parabionts, two to three months after operation, were given propylthiouracil as in Group I, until death of the two pairs at 143 and 321 days.

Thirty-six additional Slonaker rats were treated with 1.5 to 1.85 mc. of I^{131}. Of these, 15 survived only 2 to 30 days and the 21 others, including 11 male and 10 female, were observed until death at 51 to 600 days. Normal untreated parabiont controls were also examined, as well as untreated control rats, a total of 9 and 10, respectively.

All animals were observed for the development of tumors and were killed when death appeared imminent. Complete autopsies were performed, and all major organs, particularly the endocrine glands, were examined microscopically. Routine fixation in Zenker-formol, Autotechnicon processing, and hematoxylin and eosin stains were used. Pearse modified PAS stain was employed to study the pituitary glands. In Slonaker rats of comparable ages bred in this laboratory for the past 10 years, the only spontaneous neoplasms observed have been benign mammary fibroadenomas.

As anticipated from previous parabiosis experiments, mortality and morbidity following surgical parabiosis were high and resulted in the loss of 116 additional rat pairs.[7] Parabiosis intoxication occasionally developed,[8] but was not a serious problem and had no evident influence on the outcome of the experiments.

The duration of exposure to carcinogenic AAF, numbers of animals in the various groups, and additional procedures employed are summarized in Table 1 for experimental and control groups.

TABLE 1.—*Experimental and Control Rat Parabiont Groups with Duration and Dosage of Carcinogen*

Rats, No. and Sex	Duration, in Days	Total AAF, in Mg.	Parabiont Treated
Experimental			
5 F	13-29	0-5	Castrated
7 F	45-107	55-157	Castrated
3 F	127-454	230-275	Castrated
6 F	239-610	215-275	Castrated
2 F	369-599	5	Castrated
4 M	89-175	170-240	Radiothyroidectomy
3 M, 1 F	72-288	90-105	Radiothyroidectomy and propylthiouracil
31			
Controls			
4 F	29-45	None*	Castrated
3 M	161-645	None	Radiothyroidectomy
2 F	272-599	None	Castrated
6 M, 1 F	146-633	None	Radiothyroidectomy and propylthiouracil
2 M	143-321	None	Propylthiouracil
2 M	160-600	None	None
2 F	124-315	None	None
9	92-381	None	X-radiation
31			

* AAF to castrate parabiont.

RESULTS

Hemicastration.—Hyperplasia, sometimes adenomatous in type, and neoplasms, including benign adenomas, malignant tumors, and multiple primary cancers, developed in the hemicastrate series. There were no comparable occurrences in the control rats.

In Table 2 are listed the cancers, all found at autopsy in intact females treated with AAF in the hemicastrate series. Of the total

TABLE 2.—*Cancers Developing in Parabiotic Rats After 2-Acetylaminofluorene, Partners Castrated*

Rat Code No.*	Duration of Parabiosis, in Days	Total AAF, in Mg.	Cancers	Adenomas
PF 32L	310	275	Ovary, granulosa-cell carcinoma, micr. Breast, adenocarcinoma, 3.5 cm.	Pituitary, amphophile, 1.2×0.8 cm.
PF 9L	390	227	Uterus, undifferentiated carcinoma, 4.8×2.8 cm.‡ Liver, hepatoma, micr.	Pituitary, amphophile, 0.8 cm.
PF 30L	301	225	Breast, carcinoma simplex, 0.5 cm. Parotid, epidermoid carcinoma, 1 cm.	Pituitary, amphophile, 1×0.5 cm.
PF 24L	610	215	Harderian gland, adenocarcinoma, micr. Femur, osteogenic sarcoma, 3 cm.§	Pituitary, amphophile, 0.5 cm.
PF 13L	230	227	Ovary, granulosa-cell carcinoma, 2 cm.	Liver, bile duct, 2 cm.
PF 28L	288	225	Breast carcinoma simplex, 1 cm.	Breast, fibroadenoma, 1 cm.
PF 38L	360	5†	Breast, early carcinoma, micr.	Pituitary, amphophile, 1 cm. Adrenal cortex, micr.
PF 34L	660	5‖	Breast, papillary carcinoma, micr.	Pituitary, hypertrophic amphophile, micr. Harderian gland, micr.

* Explanation of symbols: PF indicates parabiont female; PCF, parabiont castrate female; L, left; R, right.
† 215 mg. of AAF to partner, PCF 38R.
‡ Abdominal metastases and spread to partner.
§ Metastasis to lungs and kidney.
‖ Also 23 ml. of peanut oil.

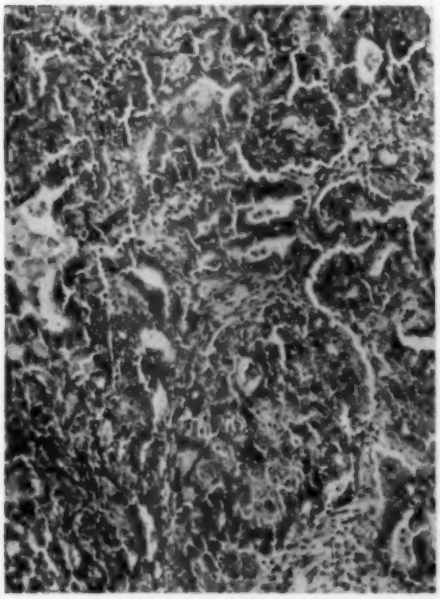


Fig. 1 (Rat PF 32L).—Adenocarcinoma of breast, developing after 310 days of parabiosis and 275 mg. of AAF. All stains except of pituitary glands are hematoxylin and eosin; reduced slightly from mag. × 125.

12 cancers in eight parabionts, 5 involved breast, 2 ovary, and 1 each liver, uterus, parotid, accessory lacrimal (Harderian) gland, and bone (Figs. 1-4). Amphophile pituitary adenomas [4] accompanied each case of multiple primary cancer (Fig. 5). Grossly the breast tumors were hard and yellow-white subcutaneous nodules. Granulosa-cell tumors were partly cystic, locally softened with yellow or brown regions. Uteri with

Fig. 2.—Granulosa-cell carcinoma of ovary, from the same animal shown in Figure 1. Reduced slightly from mag. × 125.

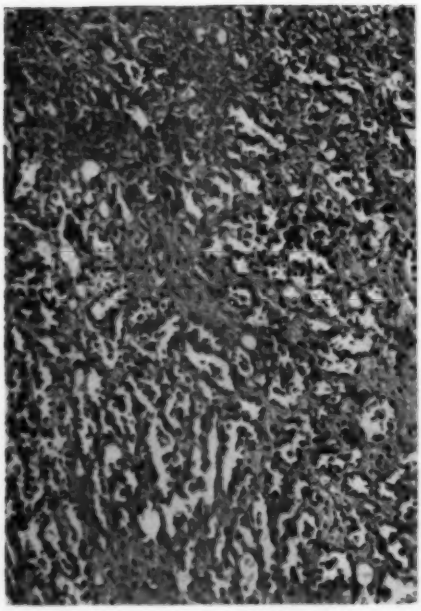
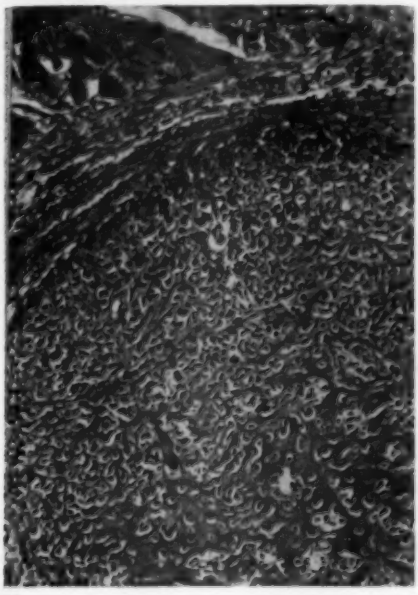


Fig. 3 (Rat PF 9L).—Undifferentiated carcinoma of uterus, found after 390 days of parabiosis and 227 mg. of AAF. Reduced slightly from mag. × 125.

Fig. 4 (Rat PF 24L).—Osteogenic sarcoma of femur, which metastasized widely, after 610 days in parabiosis and 215 mg. of AAF. Reduced slightly from mag. × 125.



hyperplasia or cancer were irregularly nodular and thickened and contained thick purulent fluid of pyometra. Liver cancers and adenomas were solid pale nodules, sharply demarcated marginally. The cancers were similar, microscopically, to experimentally produced carcinomas of ovary, uterus, breast, and liver in the literature.‡ Invasive growth and occasionally metastasis were evident, as noted also in Table 2.

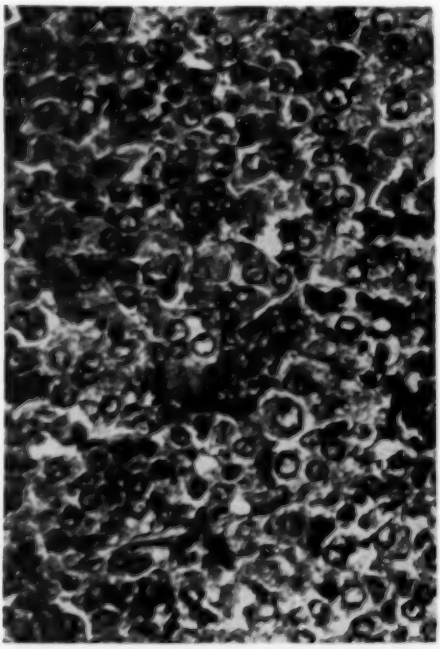


Fig. 5.—Portion of amphophile pituitary adenoma, with cell constituents lightly stained, from the same rat shown in Figures 1 and 2. Largest cells are hypertrophic amphophiles. Pituitaries stained by Pearse periodic acid-Schiff method; reduced slightly from mag. × 500.

The last two animals with breast cancers, PF 38L and PF 34L, were unusual, since they received only a single dose of AAF, through an error. The first rat was from the group in which AAF was administered regularly to the castrated right-hand parabiont, and the second from the group in which the intact rat received only peanut oil. In the case of rat PF 38L the dose of 5 mg. of

‡ References 2, 3, and 9-11.

TABLE 3.—*Endocrine Gland and Target Organ Alterations of Intact Rat Parabionts, Partners Castrated, After 2-Acetylaminofluorene*

No. of Parabiotic Pairs*	Duration of Parabiosis, in Days	Total AAF in Mg.	Ovary	Vagina Uterus	Breast	Adrenal	Pituitary	Other
5, FL	13-29	0-5	Enlarged; multiple follicle cysts; also corpora lutea	Stimulated	Neg.	Neg.	Increased basophiles	.....
7, FL	45-107	55-157	Luteinized theca of follicle cysts	Estrogen effect, pseudo-decidua	Stimulated, secretion	Hyperplasia zona fasc.	Amphophile hyperplasia	Thyroid hyperplasia Thymus, large
3, FL	127-454	236-275	Same, granulosa-cell hyperplasia	Same, pyometra	Cystic hyperplasia, ducts	Same	Same	.....
6, FL†	239-610	215-275	Same (or cancer)	Estrogen effect, polyps (or cancer)	Same, epithelial hyperplasia nodules (or cancer)	Same	Amphophile adenoma, increased hypertrophic amphophiles	Liver, bile duct cysts Nodular thyroid hyperplasia Thymus, atrophic
2, FL‡	369-500	5	Multiple follicle cysts; rete cysts	Same	Same (and cancer)	Same	Same	Nodular thyroid hyperplasia

* F indicates female; L, left parabiont.
† First 6 cases, Table 2.
‡ Last 2 cases, Table 2.

AAF was given 355 days before death, and in PF 34L it was given 483 days before death.

Endocrine glands and target organs showed various changes following AAF treatment, during the latent period of the expected development of both malignant and benign neoplasms, as well as after neoplasms had developed. These alterations are summarized in Table 3.

The production of multiple follicular cysts in the intact pair of ovaries, with later luteinization, was described by Bielschowsky.[12] Martins [13] and Witschi and Levine [14] originally described polycystic ovaries in parabiotic experiments of shorter duration. Beyond 4 months granulosa-cell hyperplasia was present, and granulosa-cell tumors occurred after 7 to 10 months (Fig. 2). Estrogenic stimulation of the intact parabiont's vaginal epithelium was evident at all intervals from 1 to 20 months, and uterine enlargement, pyometra, polyp formation, or cancer (Fig. 3) usually was associated. Breast ducts grew, acini with secretion were formed, and after four months a gross and microscopic mammary cystic hyperplasia developed. Subsequently multiple foci of epithelial hyperplasia were prominent, and sometimes cancer occurred.

The adrenal zona fasciculata cells of the intact female parabionts were enlarged, later with hyperplastic zonal thickening, and at times with nodules that bulged through the outer capsule. The thyroid gland appeared active in the first 50 to 250 days, with colloid scalloping, columnar parenchymal cells, and, later, occasionally a nodular hyperplasia. The pancreas, ampulla of Vater, and parathyroid glands appeared unchanged at all time intervals. Thymus glands first appeared large but later were atrophic.

The pituitary anterior lobe during the first month after parabiosis in the intact partner showed a relative hyperplasia of normal (gonadotropic) basophiles.[15] Beyond six weeks there was a uniform increase in pituitary amphophile cells, obscuring other cell types and producing a gross enlargement of the gland after two and one-half months of parabiosis. The amphophile cells appeared to correspond with the thyrotropic basophiles

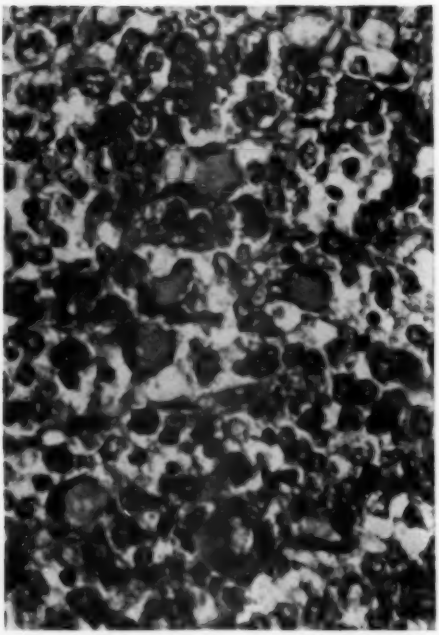


Fig. 6.—Castration cells, amphophiles, and hypertrophic amphophiles with large nuclei, from the pituitary gland of the castrated partner of Rat PF 9L, bearer of a uterine carcinoma with metastases. Reduced slightly from mag. × 500.

of Purves and Griesbach.[15] Amphophile adenomas were observed after 310 days, producing further gross pituitary enlargements and compression of the brain stem.[4] In the adenomas hypertrophic amphophile cells were numerous,[16] and sometimes predominant (Fig. 5).

Early alterations ascribable to AAF comprised moderate variations in liver-cell size with the presence of some large or multiple hyperchromatic nuclei. After seven months or more, hyperplastic and cystic changes or adenomas of small bile ducts were evident, and one malignant hepatoma of liver-cell type developed.§

Castrated right-hand parabiont rats showed few comparable changes. Their vaginas and uteri remained atrophic, and breasts were not significantly stimulated. The adrenal cortex appeared slightly nodular after two months, but without hyperplasia. Between two and three months a transient pancreatic islet hypertrophy and hyperplasia was seen. Thymus glands usually remained large. Pituitary glands of castrated females, after two months, contained numerous castration cells. An exception occurred in the castrated partners of the two rats that developed cancer metastases, where numerous pituitary amphophiles and hypertrophic amphophiles were found mingled with castration cells (Fig. 6). Slight thyroid hyperplasia developed six weeks after castration and persisted thereafter. Salivary gland ducts in these female

§ References 9 and 17.

TABLE 4.—*Benign Neoplasms in Parabiotic Partners of Radiothyroidectomized Rats and Controls*

Rat No.*	Group	Duration of Parabiosis, in Days	Age, in Days	Totol AAF, in Mg.	Total Propylthiouracil, in Mg.	Adenoma	Hyperplasias
PM 22L	III	279	...	105	1080	Thyroid, mier.	Pituitary basophiles Bone marrow Prostate
PF 91L	III	127	...	90	450	Thyroid, mier.	Pituitary basophiles
PM 12L†	...	645	...	...	...	Pituitary basophile, mier.	Thyroid Prostate
PM 51R	...	143	...	...	...‡	Thyroid, mier.	Pituitary basophiles and amphophiles
Single controls							
I 320F	...	...	510	...	...	Breast, 3 cm.	Pituitary amphophiles Breast
I 241F	...	...	576	...	...	Tubular, ovary, 0.4 cm.	.....
I 363F	...	...	600	...	...	Pituitary amphophile, mier.	Endometrium
360F	Normal	...	600	...	...	Breast	.....

* Explanation of symbols: P indicates parabiont; M, male; F, female; R, right; L, left; I, radiothyroidectomized.
† PIM 12R (partner) had 2 pituitary adenomas, 1 amphophile, 1 basophile, microscopic.
‡ Propylthiouracil, 760 mg. to partner PM 51L.

animals later frequently showed a granularity of cytoplasm supposedly normally restricted to male rodents. The parathyroid glands and ampulla of Vater appeared uniformly unchanged.

Hemicastrated pairs, when the castrated partner received AAF, after 45 days showed liver-cell degeneration and regeneration. The hemicastrate controls, when peanut oil was fed to the intact rat, had evidence of estrogen stimulation of the breast but no unusual pituitary changes. Untreated intact parabionts showed no comparable endocrine abnormalities after 120 to 315 days.

Hemiradiothyroidectomy.—Compared with the previous series, the incidence of malignant neoplasms was very low. Benign tumors observed are listed in Table 4. All except one mammary fibroadenoma occurred in the radiothyroidectomy series. Two microscopic thyroid adenomas accompanied the diffuse thyroid hyperplasia uniformly observed after propylthiouracil therapy in the parabionts that also received AAF. One thyroid adenoma developed in an intact parabiotic pair in the animal not receiving propylthiouracil. Pituitary adenomas occurred in both partners of one control pair comprising a radiothyroidectomized and intact male rat otherwise untreated.

After combined goitrogen and carcinogen treatment two- to fourfold thyroid enlargements resulted, so-called hyperemic or nodular goiters.‖ The multiple adenomas in such thyroid glands and the thyroid tumors found after radioactive iodine or iodide treatment seem to be instances of nodular hyperplasia and involution rather than neoplasms.¶ In the present series, true adenomas had a uniform structure differing from adjacent thyroid, were demarcated and encapsulated, and compressed the uninvolved gland (Fig. 7).

One malignant hepatoma arose in a male parabiotic rat joined to a thyroidectomized partner for 280 days, and after a total dose of 205 mg. of AAF. The infrequency of hepatic cancer development following radiothyroidectomy is at variance with the powerful carcinogenic activity of AAF generally found.#

In single control radiothyroidectomized rats, the endocrine and target organ changes observed are well known. Typical severe local irradiation reaction, sometimes with stenosing tracheitis, a uniform striking degranulation of pituitary acidophiles, and decreased gonadal activity occurred. Large pituitary chromophobes appeared as early as

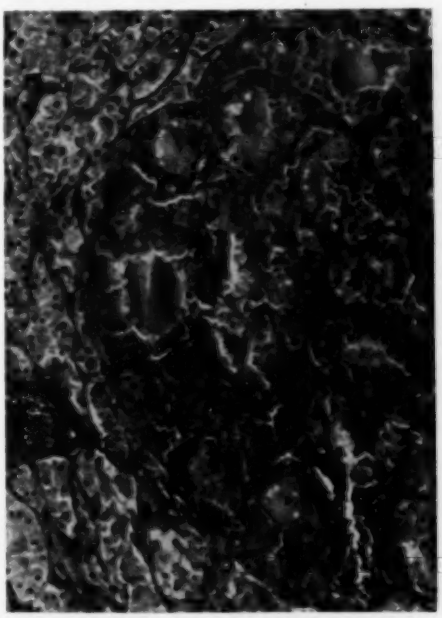


Fig. 7 (Rat PM 22L).—Follicular thyroid adenoma found after 279 days in intact parabiotic rat treated with AAF and propylthiouracil. Hematoxylin and eosin; reduced slightly from mag. × 175.

22 days and were numerous in rats of both sexes up to 273 days old. Beyond 400 days pituitary amphophiles were usually abnormally increased. Ovaries with persisting corpora lutea were typically present after radiothyroidectomy. One hyperplasia of ovarian interstitial tubules occurred at 576 days, with a sharply demarcated tubular adenoma. Beyond 400 days about half the females had in salivary ducts cytoplasmic granules supposedly seen only in normal male rodents.

‖ References 18 and 19.

¶ References 20 and 21.

References 2, 3, and 6.

I^{131}-treated parabionts with partners given carcinogen had endocrine changes like those of radiothyroidectomized single controls and comparable parabiotic control rats. Their partners that received AAF carcinogen differed from groups already described chiefly by the development of proliferative, cystic, and, rarely, hepatomatous changes in the liver parenchyma and bile ducts. No rat survived over 240 days after AAF treatment was begun.

Intact partners receiving propylthiouracil or both propylthiouracil and AAF while joined to a radiothyroidectomized parabiont had severer thyroid hyperplasia, and adenomas were found in two of four thyroid glands after both chemicals. Parathyroid hyperplasia was also evident in some older rats after propylthiouracil.[22] Basophiles were increased in two pituitary glands, amphophiles in the other two. In otherwise untreated hemithyroidectomized parabionts similar alterations of pituitary appeared at later age periods. In intact pairs one of which was given propylthiouracil unusual endocrine abnormalities were not observed. Thyroid hyperplasia was found in both partners, but was less severe in the untreated partners.

COMMENT

The technique of Bielschowsky and Hall [1] made it possible to produce most of the changes that so fascinated Gardner,[23] when he found a "tumor" mouse with multiple mammary tumors, lactating breasts, cystic hyperplastic endometrium, bilateral granulosa-cell tumors, hyperplastic adrenal cortices, and a "chromophobe" pituitary adenoma. Based on the sequences observed, this complex situation apparently took its origin in an induced pituitary-ovarian imbalance. Surgical or radiation damage to ovary may set off this reaction.* Excess gonadotropins of hypophyseal basophile origin were evidently responsible for formation of polycystic ovaries that later luteinized, developing granulosa-cell hyperplasias and sometimes tumors.[12] The persistent estrogenic ovarian secretions led to development of cystic endometrial and mammary hyperplasias. These changes comprised a primary or estrogenic phase of carcinogenesis.

The second phase consisted of a reciprocal pituitary amphophile-adrenocortical hyperfunctional state, with available evidence favoring either estrogenic stimulation or aging as setting off this secondary process. Morphologically there was a nodular hyperplasia of adrenal zona fasciculata, and a hyperplasia of pituitary amphophiles followed by formation of adenomas composed of amphophiles and hypertrophic amphophiles. The hormones involved have not been identified. Endocrine gland and target organ hyperplasias formed in the estrogenic phase were most susceptible to progressive growth as single or, occasionally, multiple cancers.

If the pituitary amphophile phase failed to develop, hyperplasias were found but no cancers. While the entire two-phase carcinogenic process in host tissues has been observed to occur spontaneously and to unfold slowly with age, carcinogens such as AAF seemed to expedite the onset and accelerate the rate. These ideas represent paraphrasing and synthesis of conclusions expressed by Bielschowsky,[26] Furth,[27] Gardner,[28] Loeb,[29] Mellgren,[16] and others.

Contrary to expectation, hemithyroidectomy failed to incite any comparable chain of events, although the intact partners developed diffuse hyperplastic thyroid enlargements from combined hormonal stimuli of both pituitary glands, in which the thyrotropic basophiles appeared increased. Thyroid-stimulating hormone produced by amphophiles is apparently not important in rat carcinogenesis in the ovary-endometrium-breast-organ group.[6] The reciprocal adrenocortical-pituitary stimulation found after hemicastration did not occur. Indications thus were that more than one type of hormone was probably produced by pituitary amphophile cells. Propylthiouracil exerted no cocarcinogenic effect.

Hall and Bielschowsky [30] in discussing thyroid carcinogenesis considered that cancer cells are first formed, then stimulated to visible growth. In hemithyroidectomized rats

* References 23-25.

given carcinogen any neoplastic cells formed evidently were lacking in the second pituitary amphophile-adrenocortical phase of stimulation, and failed to grow into tumors.

Parabiotic rat experiments have been criticized for their inherent biologic complexity and uncertainty. In our experience with over 500 parabiont Slonaker rats the variations in endocrine interreactions are relatively uniform and predictable. Parabiosis intoxication viewed as an induced hypersensitivity removes considerable mystery from incidental observations.[8] Statistical analyses involving large numbers of parabiotic animals during long-term carcinogenesis experiments, although perhaps ideal, have not yet been possible anywhere to our knowledge.

SUMMARY

The importance of gonadotropic stimuli when combined with an extrinsic carcinogen in the development of experimental cancers in ovaries and their target organs has been confirmed with use of parabiotic rats. A primary estrogenic phase of carcinogenesis was associated with hyperplasias of ovarian granulosa cells, endometrium, and breast. A secondary pituitary amphophile-adrenocortical phase was observed in association with the outgrowth of cancers. Hemithyroidectomy of parabiont pairs given carcinogen reduced the incidence of cancers.

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Induction of Melanotic Lesions During Skin Carcinogenesis in Hamsters

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Although relatively few experiments in carcinogenesis using polycylic hydrocarbons have been performed in the hamster, those on record describe a neoplastic response similar to that seen in other laboratory animals. Thus, Gye and Foulds [1] and Halberstaedter [2] induced sarcomas by subcutaneous injection of benzopyrene. Crabb [3] and Lutz and co-workers [4] obtained similar results using 9,10-dimethyl-1,2-benzanthracene, and methylcholanthrene, respectively. Schinz and Fritz-Niggli,[5] using benzopyrene, recorded the induction of the commonly seen sequence of squamous-cell papillomas and carcinomas.

The induction of melanotic tumors in mammals following treatment with both mixtures and pure chemical carcinogens has been an infrequent occurrence in the many experiments recorded in this field. Thus Lipschütz recorded pigmented foci in the skin of mice painted with coal tar,[6] and Passey [7] reported on melanomas in dogs injected subcutaneously with this material. 5,9,10-Trimethyl-1,2-benzanthracene has been reported to induce melanotic lesions in the skin of the mouse following topical application by two groups of investigators.* In the reports of Badger and his co-workers [8] no histological description was provided, but Burgoyne and co-workers [10] described their material in detail. They concluded that one tumor occurring subcutaneously in a dba mouse was a "pigmented spindle cell tumor

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* References 8, 9, and 10.

Skin Carcinogenesis in the Hamster
Results of Experiments in Which Hamsters Were Painted in the Interscapular Region

Group	Initial No. of Animals	Survivors at 15 Wk.	No. of Papillomas	No. of Carcinomas	No. of Animals with Melanotic Lesions	No. of Melanotic Lesions	Average Latent Period of Melanotic Lesions, in Wk.
I							
1% DMBA * in liquid petrolatum U. S. P. once	14	10	2	3	4	9	41
II							
1% DMBA once, 5% croton oil twice, weekly	14	12	..	1	5	9	38
III							
5% croton oil twice weekly	14	13	..	..	..	..	..
IV							
1% DMBA weekly	6	5	20	10	..	..	..

* 9, 10-dimethyl-1, 2-benzanthracene.

Fig. 1.—Hamster with large cutaneous melanotic lesion 50 weeks after application of 9,10-dimethyl-1,2-benzanthracene.

with local invasion (malignant melanoma)." Berenblum [11] has described a malignant melanoma occurring in a guinea pig after the subcutaneous injection of 9,10-dimethyl-1, 2-benzanthracene.

In several carcinogenesis studies in the mouse it has been found possible to induce tumors with a single application of a carcinogen followed by repeated applications of the promoting agent croton oil.[12] It has, however, been found that croton oil has a strong species specificity, being inactive in the rat and guinea pig. In the rabbit initial studies showed croton oil to be inactive,[12] although this has recently been disproved by prolonging the period of treatment.[13] The present experiment was undertaken primarily to study the action of carcinogen and croton oil on an additional species, the hamster. For this reason animals have been treated with a single application of carcinogen with and without croton oil. Additional control groups have been treated with either repeated applications of the carcinogen or with croton oil only.

Fig. 3.—Gross specimen of large cutaneous melanotic tumor of hamster 40 weeks after application of 9,10-dimethyl-1,2-benzanthracene.

MATERIALS AND METHODS

Fifty adult Syrian golden hamsters (Abrams Small Stock Breeders, Chicago), male and female, were used; they were housed in plastic cages and fed Rockland mouse diet and lettuce leaves ad libitum. The carcinogen used was 9,10-dimethyl-1,2-benzanthracene (Eastman Organic Chemicals), (DMBA), a 1% solution in liquid petrolatum

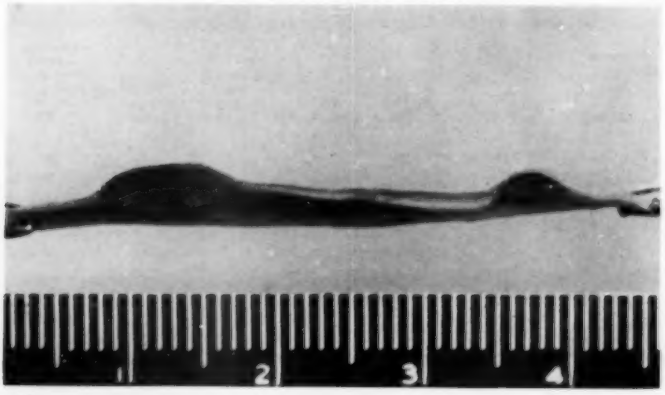


Fig. 2.—Cross section of two small cutaneous melanotic lesions.

Fig. 4.—Small melanotic lesion (about 5 mm. in the largest diameter). Note the abundance of pigment and the free zone between the epidermis and pigmented area. Hematoxylin and eosin; reduced about 2/5 from mag. × 44.

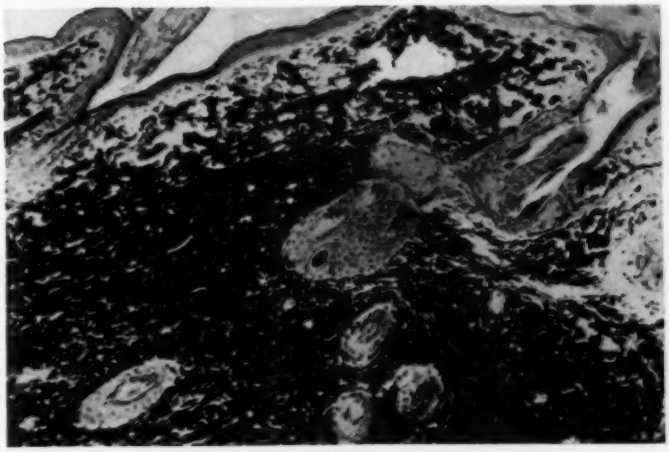


Fig. 5.—Small melanotic lesion. Hair follicles surrounded by pigmented cells stand out as pigment-free areas. Hematoxylin and eosin; reduced about 2/5 from mag. × 273.

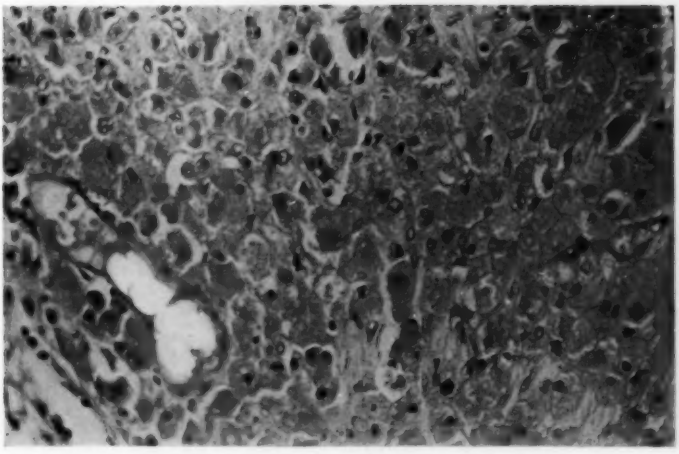


Fig. 6.—Small melanotic lesions after complete removal of pigment with potassium permanganate. Area almost entirely composed of polyhedral cells. Potassium permanganate and hematoxylin and eosin; reduced about 2/5 from mag. × 600.

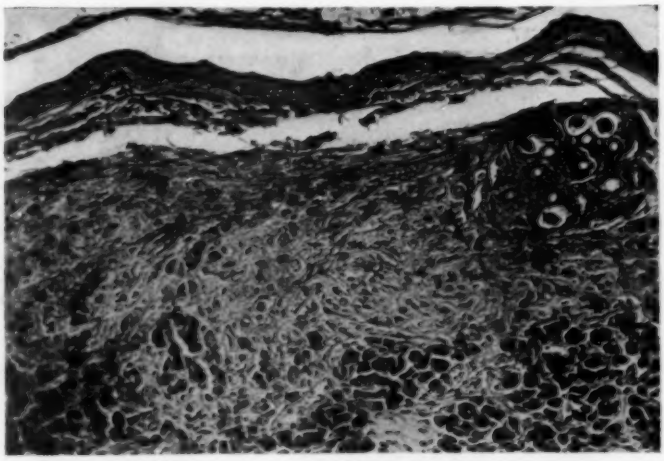


Fig. 7.—Small melanotic lesion after partial removal of pigment with potassium permanganate. Groups of polyhedral cells interspersed with spindle-shaped cells resembling fibroblasts and fibrocytes. Potassium permanganate and hematoxylin and eosin; reduced about ⅔ from mag. × 338.

U. S. P. (Superia 34, Standard Oil of Indiana); the promoting agent used was croton oil (Oleum Crotonis, B.P., Boots) 5% in liquid petrolatum U. S. P. The hamsters were shaved on the back with an electric clipper and the solution applied with a glass dropper. The hamsters were divided into four groups and treated as follows:

Group I (7 males and 7 females).—One application of 1% DMBA and no further treatment.

Group II (7 males and 7 females).—One application of 1% DMBA followed by twice weekly applications of croton oil.

Group III (7 males and 7 females).—No initiating treatment and twice weekly application of croton oil.

Group IV (4 males and 4 females).—Weekly application of 1% DMBA.

RESULTS

Results are recorded in the accompanying Table. In Groups I and II, after about 30 weeks, black spots and nodules in the painted area were noted. At the end of the experiment nine hamsters, five male and four female, had born 18 pigmented nodules, 8 measuring about 0.2 cm. in the largest diameter, 4 about 0.5×0.3 cm., 3 about 1×1×0.4 cm., and 3 about 3×2×1.5 cm. (Fig. 1). Two papillomas and four carcinomas were also obtained. No difference between males and females was noted. Transplants of the largest tumors were attempted with intramuscular and intracranial injections of

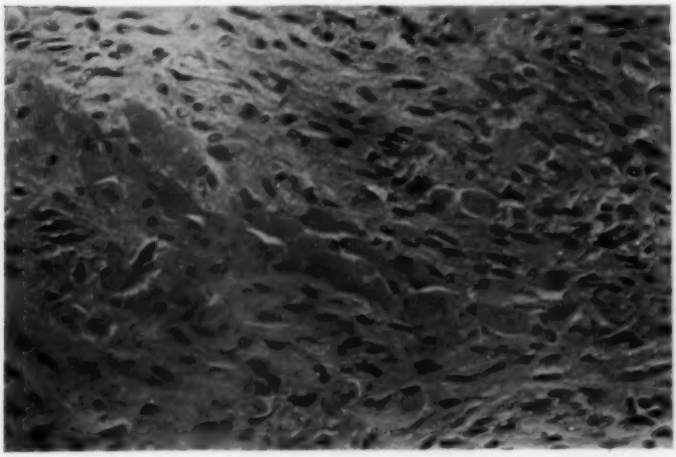


Fig. 8.—Large melanotic lesion after complete removal of pigment. This is an area in which polyhedral cells are still present even though spindle-shaped cells predominate. Potassium permanganate and hematoxylin and eosin; reduced about ⅔ from mag. × 600.

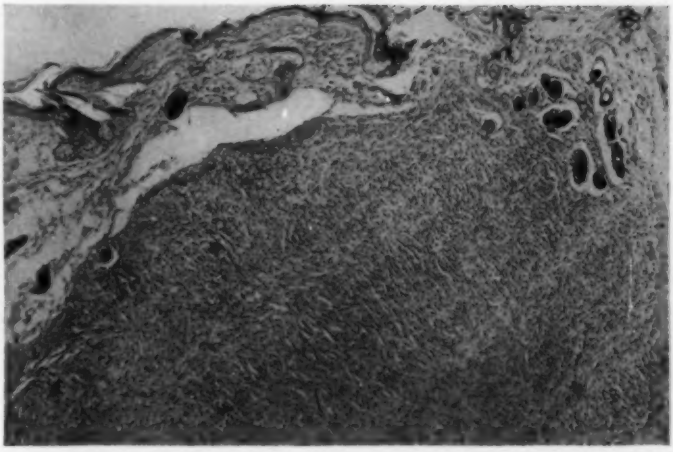


Fig. 9.—Large melanotic lesion after complete removal of pigment. Lesion almost entirely composed of spindle-shaped cells. Skin appendages incorporated in the peripheral portion of the advancing growth. Potassium permanganate and hematoxylin and eosin; reduced about ⅔ from mag. × 130.

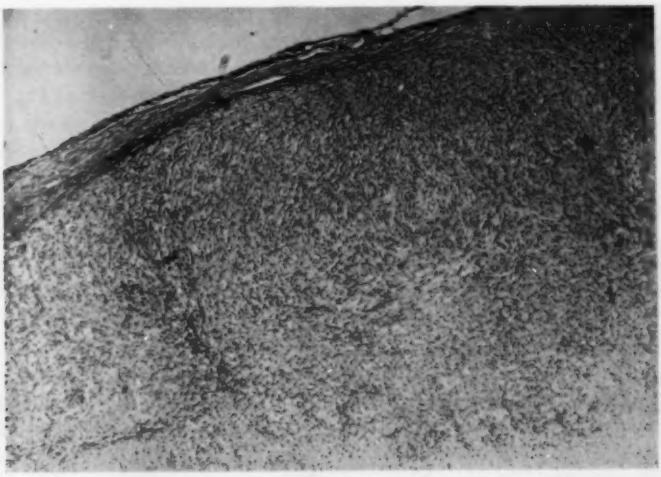
emulsified tissue and with subcutaneous insertion of pieces of the pigmented tissue. At the present time the results are negative. Group III, including 14 hamsters painted with only croton oil, developed neither cutaneous tumors nor pigmented nodules after 40 weeks of treatment. In Group IV, at the 15th week five of the eight hamsters painted weekly with DMBA had survived, and all bore some papillomas and squamous-cell carcinomas (20 papillomas and 10 carcinomas). The average latent period was 16 weeks. At the 20th week all the animals of the Group IV were dead. No pigmented nodules were noted.

The squamous-cell papillomas and carcinomas in Group IV were similar to the lesions seen in mice and rabbits † and need no additional description.

Melanotic Lesions.—The small lesions, measuring between 0.2 to 1.0 cm. (Fig. 2), were well-circumscribed, flat nodules located

† References 14 and 15.

Fig. 10.—Same as Figure 9. Note formation of capsule and early necrosis. Potassium permanganate and hematoxylin and eosin; reduced about ⅔ from mag. × 95.



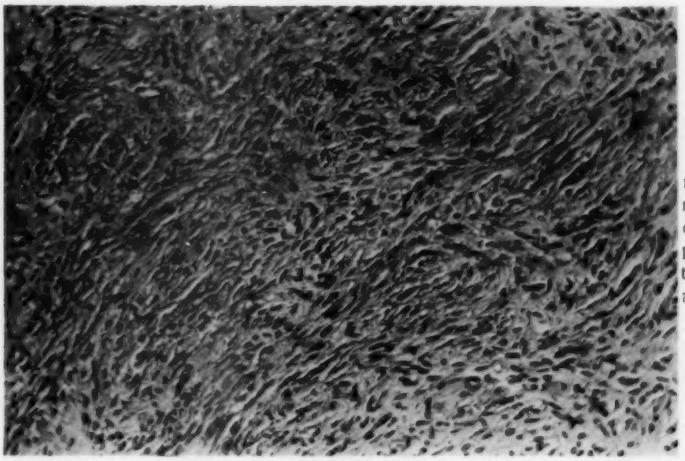


Fig. 11.—Higher magnification of large melanotic lesions after removal of pigment. Potassium permanganate and hematoxylin and eosin; reduced about ⅝ from mag. × 300.

immediately underneath the skin. On sectioned surface, they were well demarcated, ovoid in shape, and completely black in color. The large lesions measured up to 3×2×1.5 cm., had a nodular structure, were firm, appeared encapsulated, and were coal-black in color (Fig. 3). These lesions could be readily enucleated and seemed to have no direct gross connection with the skin.

Sections from the smaller lesions which measured between 0.2 to 1 cm. in diameter showed circumscribed accumulations of heavily pigmented cells (Fig. 4). The pigment was dark brown and gave a positive Fontana stain, a negative iron reaction, and could be removed with potassium permanganate. In those cells where the individual granules could be identified, they were very small and dust-like in character. While the lesions were well circumscribed, they were not encapsulated. Because of the very heavy pigmentation, cellular and nuclear details could not be discerned, except that most of the cells appeared to be polyhedral in shape. The lesion was separated from the basal-cell layer of the epidermis by a zone of collagenous tissue, which was either free from pigmented cells or contained only a scattering of pigment-bearing spindle-shaped cells closely resembling melanophores. In other areas, polyhedral cells containing varying amounts of pigmented granules were seen in the vicinity of the circumscribed pigmented lesions. These cells had the morphologic features of macrophages. Often skin appendages such as sweat glands, hair shafts, and sebaceous glands were incorporated within the pigmented lesions and, under low magnification, stood out as pigment-free areas (Fig. 5). No pigment could be demonstrated in the epithelial cells of either the epidermis or the skin appendages. Junctional changes comparable to those seen in certain nevi and most malignant melanomas of humans were not present.

To study the cellular details, sections partially and completely bleached by treatment with potassium permanganate and subsequent hematoxylin and eosin staining were examined. They showed polyhedral cells arranged in diffuse sheets (Fig. 6) and sometimes in circumscribed clusters, interspersed with spindle-shaped cells resembling fibroblasts and fibrocytes (Fig. 7). In partially bleached sections the pigment was still present in abundant amounts in the polyhedral cells without obscuring the cellular and nuclear details, whereas the spindle-shaped cells were practically free from pigment (Fig. 7).

Sections from the large lesions showed a similar composite picture of polyhedral and spindle-shaped cells (Fig. 8). The spindle-shaped cells appeared to be far more promi-

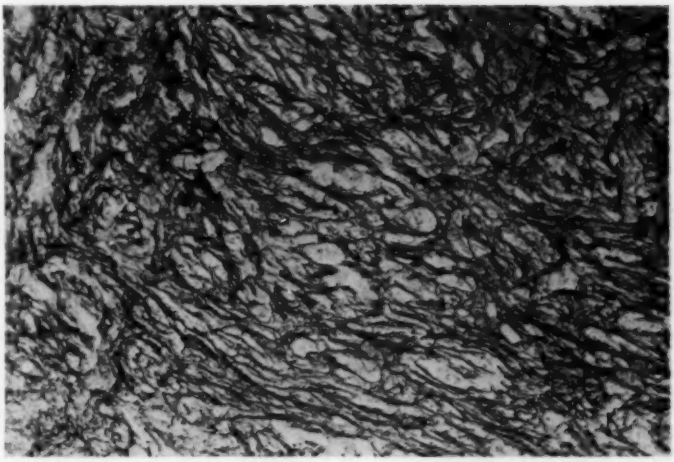


Fig. 12.—Same as Figure 11. Demonstration of reticulum fibers surrounding practically every cell. Potassium permanganate and silver impregnation (Snook); reduced about ⅔ from mag. × 350.

nent and were often arranged in interlacing bundles and whorls. In some of them the spindle-shaped component was so prominent that it imparted upon the tumor a histologic structure closely resembling cutaneous neurofibromas (Figs. 9 and 10). They had a tendency to grow about skin appendages, incorporating some in the peripheral portion of the advancing growth (Fig. 9). Focal areas of necrosis were invariably present, and sometimes extensive, sparing only the peripheral portions of the lesions. The demarcation between the periphery of the lesion and the surrounding soft tissue was even more striking than that in the smaller lesions, with compressed collagenous tissue strongly suggesting the presence of a capsule (Fig. 10).

A silver impregnation, according to the method of Snook,[10] was employed on both the small and the large lesions. There was a striking difference in the reticulum pattern of those areas in which polyhedral cells predominated and those which were composed of spindle-shaped cells (Fig. 11). In the former, groups and clusters of polyhedral cells were partly surrounded by reticulum, but the individual cells were not separated from one another by reticulum fibers. In the areas in which the spindle-shaped cells predominated, there was an abundance of finely and coarsely fibrillar reticulum with each cell completely enveloped by reticulum fibers (Fig. 12). In the necrotic areas the reticulum was completely destroyed. Masson stain showed a similar pattern with a finely fibrillar collagen material appearing between the spindle-shaped cells, completely separating them from one another. Regional lymph nodes draining the large lesions were examined with great care, but no evidence of metastasis was found. Pigmented cells within the sinuses of these lymph nodes could all be identified as macrophages.

COMMENT

Microscopically the pigmented lesions experimentally produced in hamsters bear no resemblance to malignant melanomas of the skin as observed in human material, the most important difference being the complete absence of junctional changes in the epidermis. The histologic structure of these lesions suggests that they are not of epithelial origin, but are composed of supportive tissue elements which are heavily pigmented. The fact that as the lesion grows the polyhedral cells tend to disappear and the spindle-shaped cells proliferate and become more abundant suggests that the latter represent the cell type with actual growth potential, while the former may merely be carriers of the pigment during the early phase of the lesion. While we were uncertain as to whether or not the small lesions were true tumors, particularly

since the bulk of them were made up of polyhedral cells having the morphological features of macrophages, the larger lesions had a gross appearance and microscopic structure consistent with neoplasia.

As has been previously pointed out, there was no resemblance to malignant melanoma (melanocarcinoma) of the skin of man. However, when one considers (1) the location of the lesions which spare the superficial portions of the cutis, (2) the absence of junctional changes in the epidermis, and (3) the proliferation of spindle-shaped cells arranged in interlacing bundles and whorls, a similarity with cellular blue nevi of man does exist. Following depigmentation the largest lesions bear a striking resemblance to cutaneous neurofibromas of man. This is of interest since the neural origin of blue nevi has been suggested,[17] even though we were unable to demonstrate nerve fibers within the experimental tumors by the Bodian method.

Careful study of cellular details failed to reveal any morphologic evidence to suggest that the lesions, either small or large, were actually malignant. Incorporation of skin appendages suggesting an infiltrative growth does not, in itself, prove malignancy. Similar pictures may be seen in neurofibromas in human material. No cellular or nuclear atypicalities were observed, and mitotic figures were extremely rare. However, there is one feature which should be emphasized, i. e., the presence of necrosis in the larger lesions. Necrosis is considered to be of diagnostic importance in malignant blue nevi of man,[17] but evidence that it may have the same significance in the melanotic lesions experimentally produced in hamsters is, as yet, unavailable. Transplantation experiments to demonstrate the possible malignant nature of the lesion are in progress.

It is of some interest that a single application of 9,10-dimethyl-1,2-benzanthracene gave rise to a different pathological picture from that seen with repeated applications of the same carcinogen. It seems likely that the longer survival period in the former group may have played an important role. Croton oil, which proved to be without any effect on the hamster when painted alone, did not influence carcinogenesis as a promoting agent in this species.

SUMMARY

Syrian golden hamsters were painted on the skin with either single or repeated applications of the carcinogen 9,10-dimethyl-1,2-benzanthracene.

A group of hamsters treated with a single application of 9,10-dimethyl-1,2-benzanthracene was subsequently painted repeatedly with croton oil. Another group only received the croton oil treatment.

Hamsters painted repeatedly with carcinogen developed squamous-cell papillomas and carcinomas.

Hamsters painted once with carcinogen with or without subsequent croton oil treatment developed melanotic lesions whose morphology and nature are discussed.

Croton oil proved to be without carcinogenic or promoting action in the hamster.

ADDENDUM

Since submission for publication one of the melanotic tumors has been transplanted successfully. The transplant is deeply pigmented with a histological structure identical with that described for the larger melanotic tumors. Further transplantation studies are still under way.

Miss Kay Spencer and Mr. Robert Feldman gave technical assistance. Photographs were taken by Mrs. Evelyn Palmer and Mr. Thomas Scanlon.

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Amebic Granuloma Probably Arising in Cecal Diverticulum

Report of a Case

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Amebic granuloma, or ameboma, is a localized granulomatous mass involving the large bowel which occurs as a complication of amebiasis, and which is often mistaken for carcinoma. One of the best of the early papers on the subject was written by Gunn and Howard [1] in 1931; three cases were reported and the pathology of the lesion clearly described. The best recent publication is by Spicknall and Peirce,[2] which appeared in 1954, and which included a report of four cases and a review of the literature.

Ordinarily in amebic colitis the organisms colonize beneath the mucosa and spread laterally in the submucosa with the formation of small flask-shaped ulcers. These tend to become confluent with the formation of sharply outlined ulcers with undermined edges, but the muscle coat of the bowel is usually not invaded and the process remains superficial. In amebic granuloma the organisms penetrate more deeply and a large amount of fibrous tissue is formed which produces pronounced thickening of the intestinal wall. The mucosa usually disappears with the formation of an ulcer on the mucosal side of the granuloma, which may be as large as 7 or 8 cm. The floor of the ulcer is made up of necrotic material containing amebae, and superficial and deep abscesses may be present which also contain the organisms.

This lesion is distinctly uncommon. Radke [3] found two in 96 fatal cases of amebiasis, and Spicknall and Peirce,[2] four in 214 patients. The latter authors found 230 amebic granulomas in 197 patients reported in the literature, of which 40.9% occurred in the cecum and 26.5% in the rectum and anal canal.

The clinical symptoms vary considerably, but there is often a history of intermittent diarrhea which is often bloody, and right lower quadrant pain and a palpable mass are often present in the cecal lesions depending upon the size of the granuloma. The cecal granulomas may produce rather characteristic x-ray findings on barium enema examination, which, according to Giles and Henry,[4] may permit of a presumptive diagnosis even in the absence of a palpable mass. The normal sac-like appearance of the cecum is replaced by a gradual narrowing of the cecal wall until it assumes the appearance of a cone. The walls are shaggy and irregular, and the cecum is irritable, emptying itself rapidly. In the rectum and sigmoid the lesion may be indistinguishable from carcinoma except by biopsy. Endameba histolytica in cystic or trophozoite form has been found in the stool in many of the reported cases, but failure to demonstrate the organism does not rule out amebic granuloma.

All writers on the condition stress the importance of correct diagnosis in order to avoid unnecessary surgery, and in order to minimize the risk of surgery should it become necessary for the relief of obstruction or other complications. All agree that surgery without preliminary treatment with antiamebic drugs may be disastrous because of amebic involvement of the skin, hemorrhage, exacerbation of the colitis, fecal fistula, or peritonitis. Drugs which have been successfully used in the treatment of amebic granuloma include chloroquine, emetine, chlortetracycline, oxytetracycline, fumagillin, and carbarsone; Spicknall and Peirce state that in the great majority of cases the lesion disappears within a month after the start of treatment. It goes without saying that careful

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stool examinations should be done if there is any clinical or radiologic suspicion of amebiasis or amebic granuloma, but a positive stool does not rule out the possibility of carcinoma, since the two diseases may coexist.

REPORT OF CASE

A 33-year-old Japanese war bride was admitted to Kuakini Hospital, in Honolulu, on Jan. 30, 1955, complaining of tarry stools and pain in the right lower quadrant associated with a tender mass in the same region. Her present illness began about one year before admission with pain in the right lower quadrant, which was intermittent and sometimes stabbing in character. About one month before admission a tender mass was noticed in the right lower quadrant, which slowly increased in size. The stools were soft and of normal color until one week before admission, when tarry stools were noticed for the first time.

The patient was hospitalized at the age of 9 years for "pleurisy," and at the age of 13 passed dark stools for a time but had no medical treatment. At the age of 24, she was ill with tenesmus and bloody diarrhea, and a diagnosis of amebic dysentery was made and treatment carried out. A perianal abscess developed two years later, at the age of 26, which was incised and drained. This recurred six months later, requiring further incision and drainage. Healing was complete and permanent following this.

Physical examination showed a well-developed Japanese woman who was cooperative and rational. The temperature was 100.4 F, the pulse rate 90, and the respirations 12. The conjunctivae were moderately anemic. A small healed scar was present in the submental area. There was a firm tender mass in the right lower quadrant of the abdomen which measured 10×7 cm. It appeared to be fixed to the posterior parietal peritoneum. No pulsations or bruit was noted over the mass, and the peristaltic sounds were active but did not suggest obstruction. There were no abnormal findings on pelvic examination. Rectal examination showed a healed perirectal scar and no abnormal masses of any sort. The stool was formed and brown in color, and there was no blood, pus, or mucus.

X-ray examination of the chest showed nothing unusual except a few calcified scars in the right lung field. A survey film of the abdomen showed a soft tissue mass in the right lower quadrant overlying the iliac crest which was distinct from the right kidney. Examination of the large bowel by barium enema showed no obstruction to the retrograde flow of the opaque medium. The cecum was very irritable and did not fill well, and it was displaced medially by the soft tissue mass noted above. Barium appeared in the terminal ileum, and the appendix was visualized. The impression of the radiologist, Dr. H. W. Chang, was extrinsic pericecal mass, possibly a tuberculous abscess. An intravenous urogram showed no evidence of renal disease.

Laboratory examination showed a trace of albumin in the urine and severe anemia, the red blood cell count being 2,090,000 and the hemoglobin 5.6 gm. The white blood cell count was normal. The stool was positive for occult blood. After two units of blood, the red blood cell count was 3,700,000 and the hemoglobin 9.6 gm.

The patient was prepared for surgery by giving 2 gm. of succinylsulfathiazole (Sulfasuxidine) four times a day, multivitamin preparations, 10 mg. of vitamin K two times a day for six days, and Dicrysticin (crysticillin fortified with 400,000 units with dihydrostreptomycin sulfate), two ampules daily for four days prior to surgery.

On Feb. 8, 1955, with the patient under spinal anesthesia, a right paramedian muscle-splitting incision was made. There were many diffuse web-like adhesions between the omentum and the anterior parietal peritoneum, and similar adhesions were present about the liver. In the ileocecal area, there was a grapefruit-sized solid mass involving the cecal wall throughout its circumference, with the appendix bound into the mass. Several small, soft lymph nodes were palpable in the mesentery of the right colon. The entire mass was freed after mobilization of the right colon to the midcolic artery. The terminal ileum approximately 8 in. (20.32 cm.) from the ileocecal junction was used as the site of election for resection, and a right hemicolectomy was done with an end-to-end anastomosis between the ileum and transverse colon. Prior to closure, 1 gm. of streptomycin and 600,000 units of penicillin were instilled in the bed of dissection. The postoperative course was smooth, and the patient was discharged on the seventh postoperative day.

Pathologic examination showed a large pericecal mass of spherical shape, measuring 8 cm. in diameter, together with 12 cm. of the ascending colon and 11 cm. of the terminal ileum. When the colon was opened, the mucosal surface of the cecum was intact although the mucosal folds were flattened, and there was no ulceration. The appendix was large, measuring 9 cm. in length, and it was intact. Near the base of the appendix a small opening 5 mm. in diameter was present, which extended into the center of the mass (Fig. 1). Upon sectioning, a central cavity was disclosed about 5 cm. in diameter, which was lined by necrotic degenerated tissue, and the surrounding wall was made up of very dense fibrous tissue measuring 2 cm. in thickness (Fig. 2). The pericecal lymph nodes were enlarged up to 2 cm., soft in consistency, and gray in color.

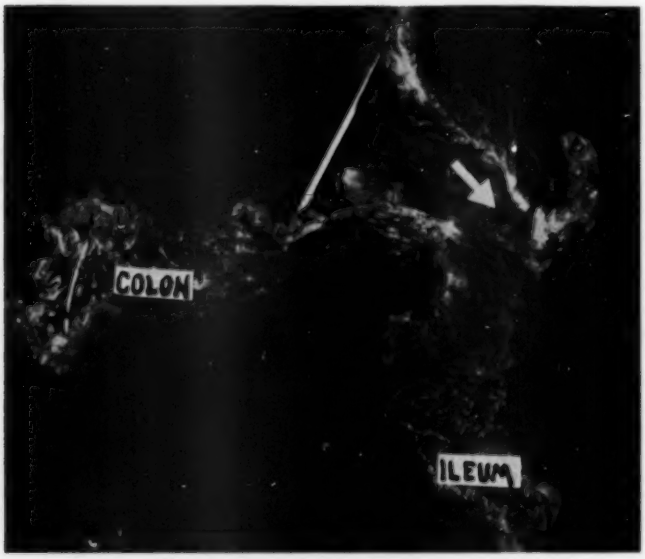


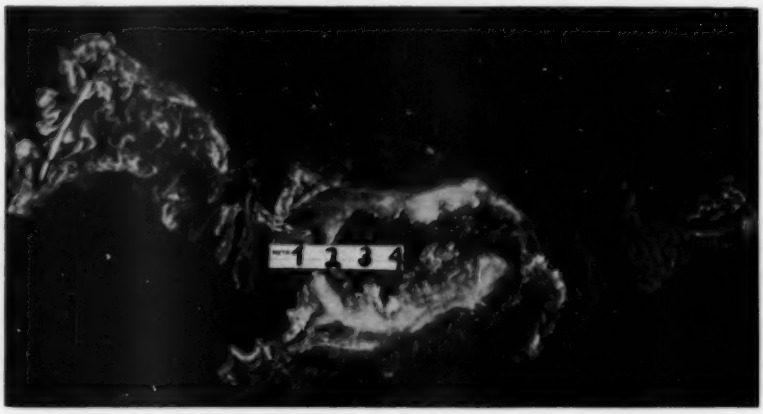
Fig. 1.—Photograph showing small opening of granuloma into lumen of cecum at the base of the appendix.

Microscopic examination showed necrotic debris lining the cavity, which contained leucocytes of various sorts and many trophozoite forms of Endameba histolytica (Fig. 3). Toward the periphery, the necrotic material was replaced by very dense acellular fibrous tissue containing scattered lymphocytes and plasma cells, with the latter predominating. The appendix showed a normal microscopic picture, and the regional lymph nodes showed nonspecific inflammatory hyperplasia. Sections taken through the small sinus between the granuloma and the cecum showed a lining of large bowel mucosa which extended inward for a distance of 2 mm. Here the epithelial lining disappeared and was replaced by granulation tissue. No organisms were present within the sinus or its inflammatory lining; they were confined to the centrally located necrotic tissue.

COMMENT

This granuloma differs pathologically from most of the cases reported in the literature by

Fig. 2.—Photograph showing necrotic center of granuloma and thick fibrous wall.



the lack of mucosal ulceration and by the small single sinus tract between the cecal lumen and the interior of the granuloma. This measured not more than 5 mm. in diameter, and it was lined for a short distance by large bowel mucosa. Because of this, it is considered likely that the process originated in a cecal diverticulum.

The organisms were confined to the necrotic zone lining the central cavity, and none were present in the lining of the sinus or in the lumen of the sinus. However, there was free communication between the interior of the granuloma and the cecal lumen, so that organisms could have been found from time to time in the feces. A preoperative stool examination was not done; postoperative examinations were negative. The severe anemia is indicative of considerable blood loss, and the history may be misleading in this respect; supposedly tarry stools had been noticed for the first time a week before admission. The history shows an attack of acute amebic dysentery in Japan nine years previously, which was treated; it is possible that the granuloma had its origin then within a cecal diverticulum, slowly increasing in size over the intervening years. The outer part of the lesion consisted of very dense fibrous tissue which was quite acellular and which was at least 2 cm. thick. Despite the opinions expressed in the literature, it is difficult to believe that a tumor with so much scar tissue in it would subside with medical treatment, even though the therapy was effective in destroying the organisms.

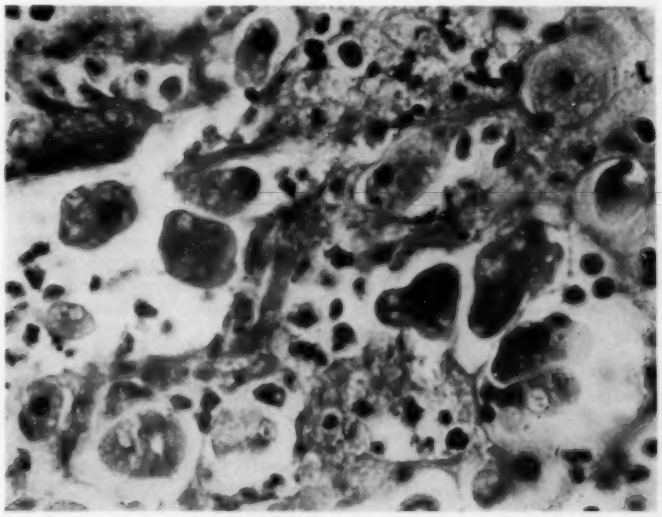


Fig. 3.—Photomicrograph showing trophozoite forms of Endameba histolytica. Iron hematoxylin; × 800.

SUMMARY

An amebic granuloma of the cecum in a 33-year-old Japanese woman is described. The pathologic features suggest an origin in a cecal diverticulum and the history indicates that it may have originated nine years previously.

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Studies on Atopic Dermatitis

II. Melanin Distribution and Dopa Oxidase Reaction

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The distribution of melanin in the skin during acute atopic dermatitis has not been studied in recent years. Furthermore, a search of the literature shows no work on the activity of melanocytes in atopic dermatitis. In his comprehensive review of the literature on the histopathology of atopic dermatitis, Alexander,[1] in 1927, stated that reports disagree concerning the increase or decrease of pigment in the basal-cell layer during the acute attack. His own histologic studies, however, revealed that in acute atopic dermatitis melanin is generally lost from the basal cells and is increased in the corium.

The present study demonstrated that the cytoplasm of epidermal cells does not contain pigment in the acute phase of atopic dermatitis, and that the melanocytes in areas of active dermatitis give a stronger dopa reaction than those in healed sites or in uninvolved skin.

METHODS

Biopsy specimens were available from 13 patients who had been studied in the first of this series of reports.[2] The group consisted of eight women, varying in age from 26 to 40, and five men, from 21 to 26 years of age; eight were white, and five were Negroes. The specimens were from sites of typical atopic dermatitis and from normal skin areas that had not been exposed to sunlight during the previous six months.

The biopsy specimens had been prepared by freeze-drying according to the method of Altmann-Gersh.[3] This method of preparation, rather than fixation with chemicals, was particularly important for the study of dopa oxidase activity of melanocytes because of its minimal effect on enzymes. After dehydration *in vacuo* at about —30 C, the frozen-dried tissues had been prepared for histologic study by infiltration with paraffin (M. P. 52 to 56 C). Multiple sections of each tissue, cut at 4μ and 8μ, were mounted on one slide for staining. This permitted an estimate of the uniformity of the sectioning. Sections of similar thickness from the areas of dermatitis and from the uninvolved skin of each patient were selected for comparative study.

The staining method used has the advantage over previous techniques in the avoidance of formalin fixation, which partially inactivates dopa oxidases.[4] In this method, mounted sections from the paraffin-impregnated, frozen-dried tissues are deparaffinized with xylene. After wiping off excess xylene, the preparation is immersed for 3 hours 45 minutes in 1:1000 buffered dopa solution (pH 7.4). A semiquantitative reaction occurs, so that specimens of approximately the same thickness can be compared and graded from 1+ to 4+ on the basis of intensity of the dopa stain. Since, in the epidermis, only the melanocytes stain with dopa, the preparations may likewise be studied for melanin distribution.

RESULTS

Melanin Distribution.—In the areas of dermatitis the scarcity of melanin granules within the epidermal cells was related to the degree of epidermal edema. In acute lesions with marked edema melanin granules were completely absent within the epidermal cells. This was true for both white and Negro patients, but was more strikingly demonstrable in the latter (Fig. 1*A*). The widened intercellular spaces were filled with fine granules, presumably within dendrites of melanocytes, but no melanin could be found inside the basal cells in acute lesions. When epidermal edema was less severe, as in one patient with subacute to chronic atopic dermatitis, a moderate number of pigment granules were present within the basal cells as well as in the intercellular spaces (Fig. 1*B*). When no edema was present, as in one patient with spontaneously healed atopic dermatitis (Fig. 1*C*), the pigment within the epidermal cells was abundant and arranged in "supranuclear

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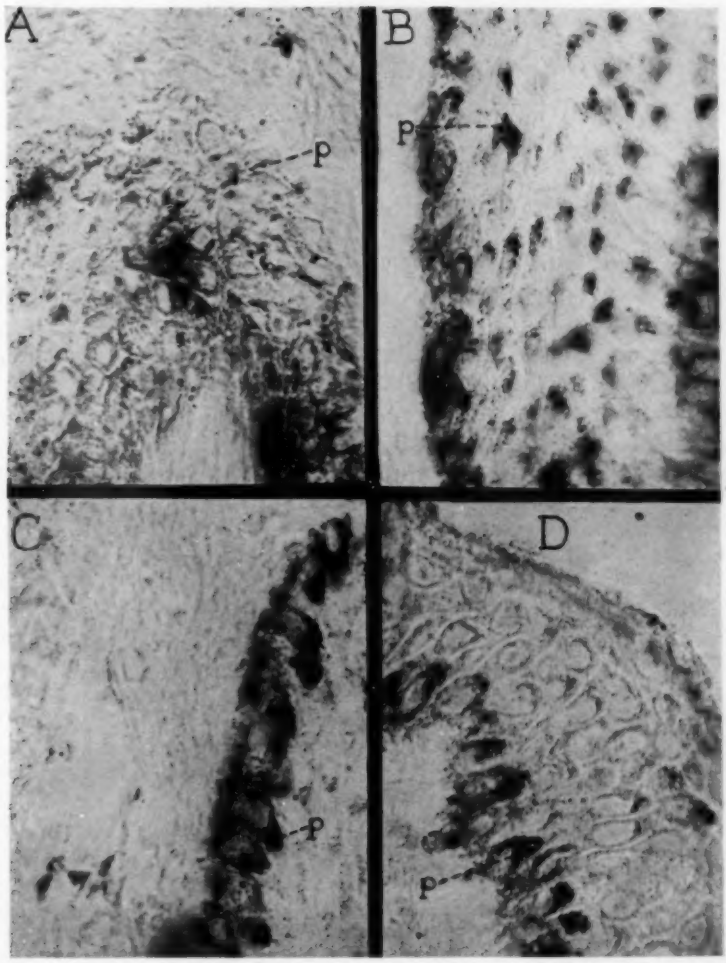

Fig. 1.—Sections from areas of atopic dermatitis and normal skin of Negro patients to show the distribution of melanin in relationship to the acuteness of the lesions. The sections were stained with dopa and photographed at × 360.

Compare the distribution of the pigment granules (*p*) in the various sections. In *A* (acute atopic dermatitis), the epidermal cells contain no melanin. The granules are outside the cells in the widened intercellular spaces. In *B* (subacute atopic dermatitis), melanin is present within the cells as well as in the intercellular spaces. In *C* (healed, slightly lichenified area) and *D* (normal skin), the melanin is similarly distributed within the basal cells.

Chromatophores (*c*) are present in all sections.

caps" characteristic of the distribution in normal skin of Negro patients (compare *C* and *D*, in Fig. 1).

The dermis of both white and Negro patients in all stages of the lesions contained a similar number of chromatophores filled with melanin granules of varying sizes.

An unusual finding in the normal skin of the eight white patients was abundance of pigment in the cells of the Malpighian layer. This was particularly noteworthy in six of this group who had lightly pigmented skin and blond hair. The dermis of the normal skin of the white as well as that of the Negro

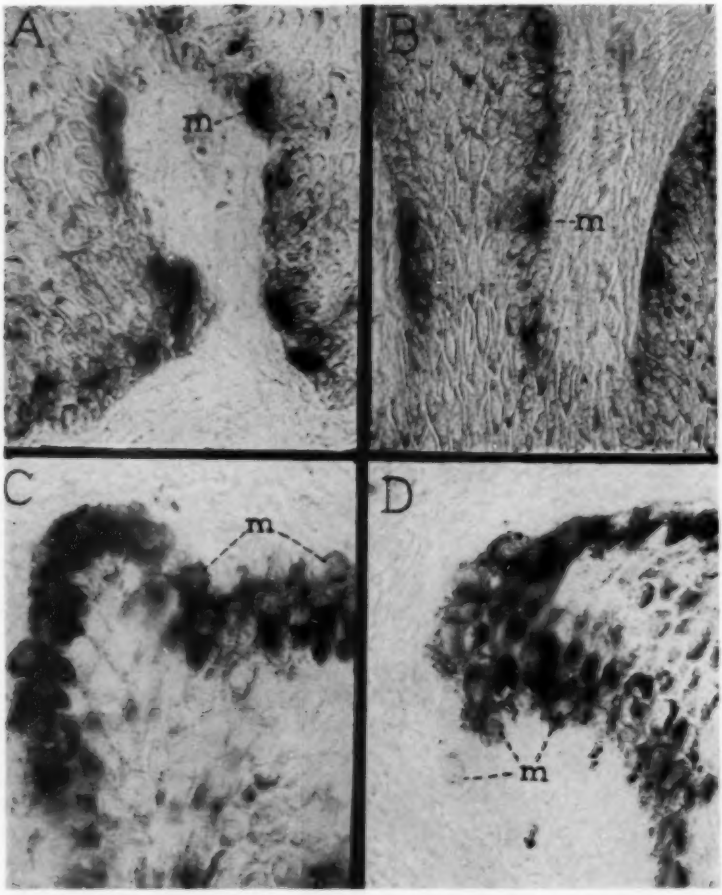

Fig. 2.—Sections from four Negro patients stained with a semiquantitative dopa method to show the variation in staining intensity of melanocytes at various stages of atopic dermatitis. All sections were photographed at the same magnification, × 360.

Compare the staining intensity of melanocytes (*m*) in acute atopic dermatitis (*A*), in subacute (*B*), in a healed, slightly lichenified area (*C*), and in normal skin (*D*). Note that the staining intensity of melanocytes decreases with the subsidence of the inflammation and that in the healed area (*C*) they stain only slightly more than in normal skin (*D*).

patients contained many chromatophores filled with melanin.

Melanocytes

The intensity of the dopa reaction of melanocytes in atopic dermatitis was related to the acuteness of the lesion; it was greater in acute (Fig. 2*A*) than in subacute (Fig. 2*B*) dermatitis. It was less in "healed" areas showing only slight lichenification (Fig. 2*C*), and least in normal skin (Fig. 2*D*).

Comment

The absence of melanin within the basal cells in acute atopic dermatitis appeared to be related to the intracellular and intercellular edema. Masson [8] stated that melanocytes act as "cytocrines"; through their branched dendrites, which are in direct contact with the Malpighian cells, melanin is inoculated into these cells. It seems likely that widening of the intercellular spaces resulting from epidermal edema breaks the contact between

dendrites and Malpighian cells, thus preventing transfer of melanin to epidermal cells. Further, edema of the Malpighian cells may produce changes in their protoplasm which prevent reception and storage of pigment. The excessive pigment which is formed in atopic dermatitis fills the intercellular spaces and flows directly into the dermis, where it is ingested by chromatophores. The process of phagocytosis appears to be rapid, since free melanin was seldom found in the dermis.

In white patients it was surprising to note the abundance of melanin in uninvolved skin that had not been exposed to sunlight for at least six months. None of the patients in this group had any recollection of an attack of generalized atopic dermatitis that might account for this. To the best of their knowledge, the lesions had always been limited to the flexural areas of the arms, the popliteal regions, the face, and, in three cases, the neck. Despite this, all of them showed much pigment in the basal cells and a large number of melanin-filled chromatophores in the dermis. While numerous causes of nonspecific irritation may stimulate melanocytes to increased pigment formation, its frequency in uninvolved skin of patients with atopic dermatitis suggests the possibility either that these persons have an increased tendency to itching even in normal areas, or, less likely, that their melanocytes are more active and more easily stimulated than those of normal persons.

It has long been recognized that a variety of causes of skin irritation will increase pigmentation. It is therefore to be expected that areas of dermatitis should show greater dopa oxidase activity than uninvolved skin. One may speculate whether the failure of pigment storage in the epidermis due to intercellular and intracellular edema may also contribute to increased melanocyte activity. In normal skin with the terminal divisions of the dendrites in contact with Malpighian cells, the process of transference and storage of pigment within epidermal cells may act as one of the regulating mechanisms for the rate of pigment formation in melanocytes. Such hypothetical control would be lost when intercellular edema separates dendrites from epidermal cells so that pigment flows directly into the dermis.

SUMMARY

1. Histologic study of atopic dermatitis showed that failure of pigment storage in epidermal cells is related to the degree of intracellular and intercellular edema of the epidermis.

2. It is suggested that the edema results in a break of contact between basal cells and dendritic processes of the melanocytes, interfering with inoculation of pigment into the epidermal cells. As a result, melanin flows directly into the dermis and is ingested by chromatophores.

3. The uninvolved skin of patients with atopic dermatitis showed an increase in pigment storage within the basal cells and in the chromatophores of the dermis.

4. The melanocytes in areas of atopic dermatitis reacted more strongly with dopa than those in uninvolved skin of the same patients.

Dr. Francis E. Senear, Professor of Dermatology, Emeritus, University of Illinois College of Medicine, selected patients from his service for this study; Dr. Samuel M. Bluefarb, attending physician, and Dr. Leonard Hoit, resident, Dermatology Department, Cook County Hospital, selected patients from their service for this study.

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Primary Intracerebral Pleomorphic Reticulum-Cell Sarcoma

Report of a Case

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In reviewing the literature one finds a multitude of titles for tumors which are identical with or closely related to the present case.* Comparison of published cases is difficult, since different criteria and nomenclature are used by various authors and photographs do not necessarily give the overall picture. Prior to 1926 many primary brain tumors were referred to as sarcomas. In that year Fried [1] reviewed 400 cases of tumors of the brain, few of which could be classified as sarcomatous. A transition in diagnoses occurred along with the improved methods of identification of brain tumors, so that the diagnosis of primary sarcoma of the brain was then rarely being made. Fried postulated that the tumor in his case originated from the adventitial cells of the Virchow-Robin space, in other words, the mesenchymal elements of the brain. The disappearance of the term "primary sarcoma of the brain" from the literature is generally credited to Bailey,[22] who with Cushing, in 1926, correlated the clinical and histologic aspects of brain tumors and differentiated between glial and mesodermal elements. Later he reported on the intracranial sarcomatous tumors of leptomeningeal origin and gave an excellent definition of primary sarcoma of the brain.[2] It is of particular interest that one of the cases reported by Bailey [2] had been reviewed in 1911 by F. B. Mallory, who described the brain tumor and indicated that the characteristics were similar to those more commonly seen in tumors belonging to the lymphosarcoma or malignant lymphoma. Bailey had observed that the distribution of reticulum in such tumors was the same as in metastatic tumors, and that it was never present in the gliomas. In 1938 Yuile [8] reported that he could identify his case of reticulum-cell sarcoma with only two other cases that had been described in the literature up to that time but would not commit himself in regard to the present case.† He discarded many published cases because of the lack of proof that the tumors were primary within the brain. It is generally agreed that the tumors described as reticulum-cell sarcoma, lymphosarcoma, or Hodgkin's disease are closely related and probably arise from the same elementary cell. Mankin ‡ found that essential Hodgkin's cells grow like reticulum cells in cultures and even display phagocytosis. There are features in the present case which are comparable to those of a number of differently described cases.

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From the Department of Pathology, U. S. Veterans Administration Hospital, Portland, Ore.

* References 1 through 21.

REPORT OF CASE

A 25-year-old white male carpenter-farmer was admitted to the Veterans Administration Hospital, Portland, Ore., on Feb. 21, 1952, as a transfer from the psychiatric hospital, Roseburg, Ore. The following history was obtained from the records of the latter hospital and from his wife.

At the age of 8 years he was reported to have had "St. Vitus' dance" for one year. He had been well until about January, 1951, when he noted difficulty in focusing his eyes and had occasional bouts of nausea and anorexia. In July, he had recurring episodes of depression, confusion, som-

† Yuile, C. L.: Personal communication.

‡ Mankin: Cited in reference 23.

nolence, and disorientation. Although these symptoms became progressively worse, he was able to continue work, except for a period of 10 days, until December, when he sought medical care and was admitted to a local hospital. On Dec. 11, a complete physical examination by a personal physician in Portland apparently indicated that there was no intracranial lesion and that the slight pupillary inequality was of little significance (right was slightly smaller). However, the fundi were not visualized, through lack of patient cooperation. He was well nourished, in fairly good contact, well oriented in all spheres, but appeared slow and mentally retarded. Blood pressure was 120 systolic and 76 diastolic. All other systems apparently were free of abnormal findings. On Dec. 30, the spinal fluid pressure was 170 mm. of water, opening; 120 mm., closing. The spinal fluid was clear and colorless. The Queckenstedt test on the right and left gave a rapid rise and fall. The fluid contained 5 erythrocytes per cubic millimeter and 34 mg. of total protein per 100 ml. The serology tests were negative. The electroencephalogram following electroshock therapy was abnormal, with paroxysmal activity suggestive of a convulsive disorder. Considering him a psychiatric case, his physician had him voluntarily admitted to the VA hospital at Roseburg on Jan. 7, 1952. The patient was aware of his altered thought processes following electroshock therapy. Varying degrees of poor coordination were observed in his walking, eating, and dressing. These became progressively worse. An organic disease was suspected, and the patient was transferred to our hospital for detailed study on Feb. 12.

The electroencephalogram, on Feb. 25, was diffusely abnormal and indicative of a diffuse physiologic disturbance. A pneumoencephalogram, on Feb. 28, was interpreted as showing a marked displacement of the left anterior horn to the right and downward, probably due to a space-occupying lesion in the left frontal area. On March 4, a left frontotemporal exposure revealed a normal dura. A firm diffuse infiltrating tumor in the left frontal lobe involved the head of the caudate nucleus and was not all resectable. On March 7, he was found semicomatose, resistive, with posturing and mannerisms much like those of catatonic schizophrenia. He remained comatose postoperatively, with a persistently elevated intracranial pressure, and died March 17. Dr. Walter A. Haug and I, on the original surgical specimen, considered the possibility of an undifferentiated metastatic carcinoma, leukemic infiltration, or metastatic lymphoma (52-T-398).

Cammermeyer,[24] of the Armed Forces Institute of Pathology, also considered it poorly differentiated and regarded it as malignant lymphoma, probably metastatic in origin, but referred to the possibilities of a primary lymphoma of the brain.

At postmortem examination there was a gush of fluid when the calvarium was removed from the site of the operative wound at the left frontal area. There was no evidence of extradural, subdural, or subarachnoid hemorrhage, and the meninges had no tumor infiltration. There was a 5×5×5 cm. surgical defect in the left frontal lobe, which extended into the anterior horn of the left lateral ventricle. Serial coronal sections revealed tumor-like infiltration of the left caudate nucleus, thalamus, and cerebral peduncle and partial compression of the third ventricle on the left. The infiltration extended to the mammillary bodies, and less prominently into the caudad aspect of the right basal ganglia, and caudally on the medial aspect of the left temporal lobe below the posterior horn. The ependymal lining of the left ventricle was finely nodular. The arteries at the base of the brain were essentially free of sclerosis. There was no evidence of any tumor, whatsoever, in any of the other organs and nothing to indicate that we might be dealing with a metastasis. Infarction was grossly ruled out, since a diagnosis of a neoplasm had been made at the time of surgery. There was, however, a phlebothrombosis of the right calf veins, and an old pulmonary infarction of the right lower lobe on the lateral surface and a recent, massive, pulmonary embolism occluding both main branches. The heart was within normal limits and the foramen ovale was closed. The blood and marrow studies had precluded any thought of a leukemia. An inflammatory condition did not appear to prevail grossly except for the reactive tissue change following surgical intervention.

The over-all histologic structure of the tumor has been well represented in the illustrations. The geographic formation as shown in the lower power was produced by an ischemic necrosis between the islands of the perivascular tumor growth (Fig. 1). It was noted in this view that there was no capsule formation, no brain tissue compression, and that the tumor cells extended toward the periphery, especially in the perivascular spaces. From this view one could readily conceive that we were dealing with an inflammatory process. However, even at this low power one could see dark bodies, more particularly toward the periphery. In the next magnification the vessel wall and, particularly, the perivascular space were replaced at least in part by the smaller cells

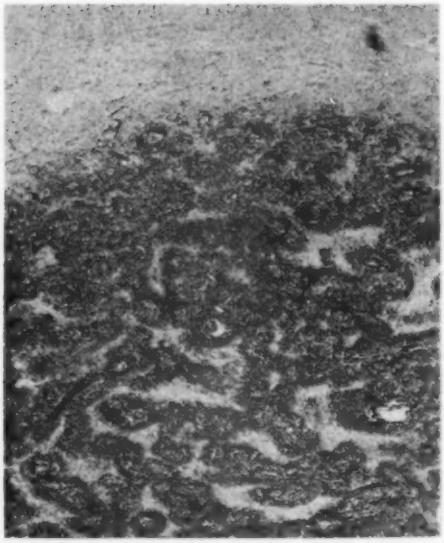
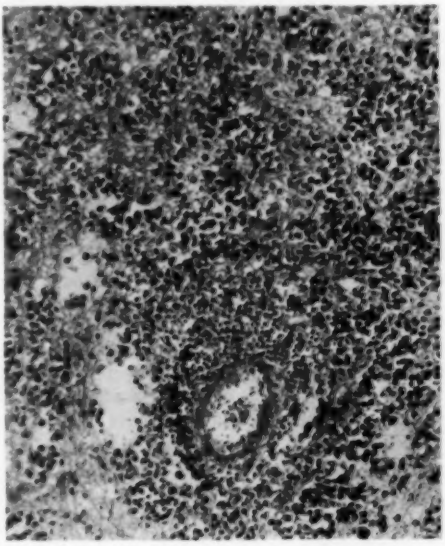


Fig. 1.—Perivascular arrangement of tumor with intervening necrotic tissue.

which still could be taken for an inflammatory infiltration (Fig. 2). The endothelial cells of the vessels generally were intact, but the walls of the vessels varied in their involvement by the tumor cells. The glial membrane generally was destroyed, and the tumor, as shown, extended singly and in clumps into the surrounding brain parenchyma. It was also noted that the cells within the parenchyma in contrast to those about the vessel were generally larger but relatively uniform in size. In the next higher power multinucleated cells were observed, in considerable numbers, especially in certain areas (Fig. 3). Here there were marked cell variations in size, structure, and staining qualities, as well as multinucleated cells which measured up to at least 25μ in diameter. The nuclei of these tumor giant cells varied in size and shape within a single cell. The chromatin of the nuclei in general was coarse, and there were from one to three prominent nucleoli. Mitotic figures were seen in virtually every high-power field. Some of the cells were almost filled with various-sized dark nuclear fragments. Microglia were few in the viable tumor, but gitter cells were numerous in the necrotic areas. The cytoplasm of the tumor cells was generally scant and often ill-defined, amphoteric, or moderately acidophilic. There were a few cells which had a considerable amount of acidophilic cytoplasm. At the periphery, and more rarely about the vessels, one might observe a few cells which had a tadpole-like arrangement, with the nucleus in the enlarged portion. The over-all picture of the tumor in this view closely resembled Hodgkin's disease, only there was a relative lack of leucocytes. The pleomorphism and the general appearance of the cells, however, were more in line with a reticulum-cell sarcoma. Neurones were destroyed by the tumor infiltration and necrosis.

In the silver preparation, one observed reticulin fibers running in all directions between the cells and joining with collagenous bundles (Fig. 4). There never appeared to be any consistent pattern or arrangement of these fibers in relation to individual cells or with clumps of the tumor growth. Occasionally, the fibers appeared to become a part of, or entangled among, the tumor cells. The fibers in the adventitial area or perivascular spaces generally appeared to be

Fig. 2.—Incomplete destruction of vessel by tumor, obliteration of perivascular space, and diffuse parenchymal infiltration.



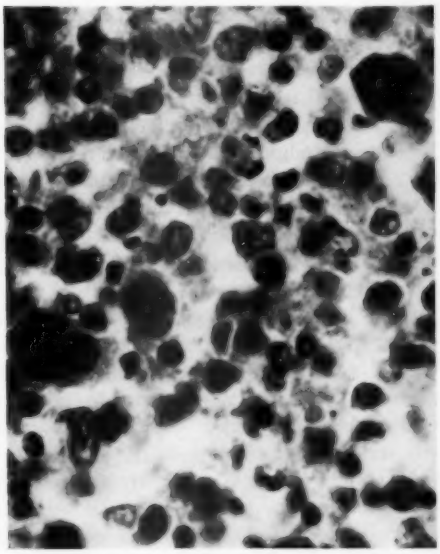


Fig. 3.—Note pleomorphism and multinucleated tumor cells.

remnants of the adventitia and were not considered as a new growth. As depicted in the photograph, some of the vessel walls appeared to have been partially disrupted by the tumor cell infiltration. The smaller cells in and about the vessels could easily have been interpreted as lymphocytes, but close observation revealed a gradual transition to the larger tumor cells in the parenchyma.

The tumor growth as illustrated did not have the characteristics of the usual metastasis to the brain from an extraneous source. The first impression of an inflammatory reaction was dispelled.

COMMENT

Fried,[1] Bailey,[2] Környey,[5] Scheinker,[6] Yuile,[8] Schöpe,[9] Hsü,[10] Abbott and Kernohan,[11] Kinney and Adams,[13] Sparling and Adams,[14] Troland and co-workers,[17] Wilke,[18] Gerhartz,[20] and Geréb[21] have reported primary tumors of the brain which were either duplicates or quite similar to the findings in the present case. The details of other cases found in the literature were not fully comparable.§

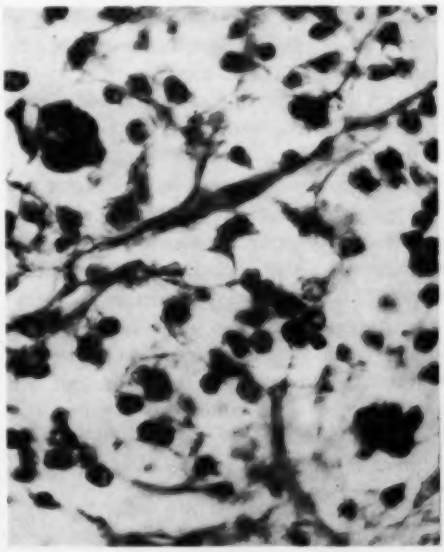
§ References 3, 4, 6, 12, 16, and 19.

In accordance with the case reports in the literature the following titles had to be considered, allowing for clinical and morphological variations: intracranial Hodgkin's disease, primary mesenchymal tumor of the brain, lymphosarcoma, reticulum-cell sarcoma, reticulosis, reticuloendotheliosis, reticuloendotheliomatosis, primary fibroreticulosyncytiales retothelsarcoma, perithelioma, periendothelioma, and diffuse perivascular sarcoma. Haymaker[25] preferred to call the tumor of my case a "primary intracerebral pleomorphic reticulum-cell lymphosarcoma of perivascular origin."

Clinically the findings are bound to vary with the location, rate of growth of the tumor, and psychosomatic status of the patient. Wilke observed that his cases did not agree clinically with any known syndrome. In general, the German authors speak of a *"raumbeschränkenden Prozess,"* which, of course, would apply to any type of tumor within the cranial vault.

There has been a considerable amount of discussion by the various authors as to the

Fig. 4.—The reticulin and collagen formation and the relationship to the tumor cells. Note giant cells. Silver stain.



origin of the cells from which these tumors arise. Bailey [2] was the first to implicate the microglia. To Yuile,‖ the tumor cells in his case displayed histologic characteristics of transitional forms of microglial cells, and, furthermore, he considered it evident that the mesodermal origin of his tumor suggested a possible relationship to the microglia. Kinney and Adams,[13] on the other hand, said that it was the consensus that the microglial cells do not undergo neoplastic changes and that, in the cases called such, the diagnosis was made because of the presence of a large number of microglial phagocytes throughout the tumor. It was their impression that the reticulum-cell sarcoma stemmed from either the reticulum cell or the histiocyte and that theoretically the histiocyte (perithelial) or the microglial cells could give rise to the reticulum-cell sarcoma. They considered that they were being conservative in calling their case a reticulum-cell sarcoma.

Hsü [10] said that there was no adequate evidence that the microglia, leucocytes, or endothelium of the blood vessels played any role in the formation of these tumors, but it was conceived that the latter arose from the leptomeningeal tissue. Abbott and Kernohan [11] reviewed the literature up to 1943 and found only an occasional reference to primary sarcomata of the brain after 1926. They reported 12 additional cases from the Mayo Clinic. They also found it impossible to determine the nature of the tumors, so frequently and erroneously masked under various modifying terms in the literature. They stated that either the tumor was rare or pathologists were reluctant to admit such a diagnosis. Three of their cases were intracerebral fibrosarcomas; seven were perivascular sarcomas; two were listed as unknown types. Kinney and Adams, in 1943,[12] reported a tumor which they said had the appearance of a reticulum-cell sarcoma (or Hodgkin's disease). In their opinion, such a tumor resembled and had a common origin with the histiocytes; also, that the reticulum formed was the same as elsewhere, namely, fibroblasts, which were stimulated by the tumor cells. In 1946, Sparling and Adams [14] reported a tumor which had the characteristics of Hodgkin's sarcoma, and they were certain that the brain was the primary site. They also referred to the close relationship of Hodgkin's disease with reticulum-cell sarcoma. They believed that the tumor originated from the reticulum cells about the vessels. Their case was the first reported of primary Hodgkin's sarcoma of the brain. Russell, Marshall, and Smith [16] described cases of perivascular proliferation and the well-marked lymphocytic cuffing of the vessels, reminiscent of encephalitis. They observed mitotic figures, necrosis, a vigorous microglial reaction, plasma cells, and various microglia-like cells. They held untenable the conception of infiltration by microglial cells into tumors which have been described as gliomas or sarcomas. They further stated that the use of the term "reticulum-cell sarcoma," as used by Yuile, and Kinney and Adams, appears based on confusion. The term "reticulosis" appeared justified by them, since they considered that all seven of their cases were predominantly of the microglial type. Their photographs, however, show reticulin fibers and compare favorably in this regard with the present case. In 1950, Wilke [18] referred to the inflammatory new growth which extended out from the adventitial elements and offered also the consideration of a fleeting transition to the blastomatous disease. His cases were classified as (*A*) inflammatory reticuloendotheliosis (*granulomencephalitis*); (*B*) reticulum-cell sarcoma (*adventitielle Sarcome*) with a lymphocytic component or a polymorphous structure. One of his cases showed the reticulin formation. He said that morphological, but not quite similar, cases were described by Foot and Cohen; Yuile; Ferens; Hsü; Benedek and Juba; Kinney and Adams; Sparling, Adams, and Parker, and Russell and co-workers. Also, in 1950, Troland, Sahyoun, and Mandeville [17] reported five cases under the heading of pri-

‖ Reference 8, and Yuile, C. L.: Personal communication.

mary mesenchymal tumors of the brain. Under this heading they included giant follicular lymphoma, reticulum-cell sarcoma, Hodgkin's sarcoma, perithelial sarcoma, and spindle-cell sarcoma. They preferred to classify reticulum-cell sarcoma and Hodgkin's sarcoma as histiocytic sarcoma. The photomicrographs of some of their cases closely resembled the one reported in this study, including the pleomorphism. They considered that the reticulin fibers are not a part of the tumor but related to the blood vessels. Geréb,[21] in 1953, preferring the term "reticuloendotheliomatose," presented a series of cases in which he believed that he could trace the changes from that of an inflammatory process to blastomatous activity. He spoke of the presence of glial reaction and of other inflammatory elements. His description of the cytological details and the manner of infiltration, along with the photographs, all tied in very closely in similarity to the case under discussion. The reticulin in his case was very clearly depicted. Like others, he compared the similarities of his case with those described in the literature and attempted to reach a satisfactory comparison. He said that despite Wilke's discussion he would like to hold to the differentiation between inflammation and tumor. He wrote that even though the impression in many cases was that of an inflammatory process, he believed that a closer examination would reveal a tumor process. Geréb [21] also believed that the starting point of these tumors was the perivascular space adventitia, because of (1) the size of the nuclei, (2) the intermingling of lymphocytes, and (3) the fact that the nuclear structure indicated that the cells arose from the proliferating adventitial mesenchymal stroma. He believed that there was a near relationship of his case with the other mesenchymal tumors of the brain.

Thus, it becomes apparent that although all are agreed that there is such a thing as a primary sarcoma of the brain, there is no unanimity of thought to taxonomy. The authors who have written a report as the first and only case unwittingly have not given due credence to previous cases that were similar in character but dissimilar in terminology. Undoubtedly, there are other unreported cases. All future cases should receive a most thorough analysis, with comparisons, and should be sent to a number of neuropathologists, if this problem is to be resolved. Although the present title is bulky and varies from those previously described, it is my belief that the present case, as previously mentioned, has many points which are similar to others and that, in general, we are dealing with a sarcoma of the brain which has a considerable variation in detail. The reticulin, pleomorphism, manner of infiltration, location, apparent source of the cells, along with the clinical history, tend to relegate many of these cases into a common denominator. The unwieldy terminology will probably become greatly simplified. Scheinker [6] believed that these tumors could be characterized by (1) diffuse extension of the tumor cells over a large area of the brain along the vessels without leptomeningeal involvement; (2) a definite malignant character of the tumor, with (*a*) an early destruction of the glia membrane with infiltration of the brain parenchyma by the tumor and formation of solid areas, (*b*) variations of growth, (*c*) lack of differentiation and polymorphism, and (*d*) many mitoses. He preferred the term "diffuse perivascular sarkome."

SUMMARY

A case of primary intracerebral pleomorphic reticulum-cell sarcoma is presented along with a discussion of similar and related cases from the literature.

Dean C. Altman, photographer, and Frank G. Bennett, librarian, gave valuable suggestions and cooperation in this study.

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Scientific Exhibits

MYOCARDITIS

A Frequent Complication of Systemic Diseases

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IN THE last few years renewed interest has been manifested in the pathology of the myocardium and the morphologic changes exhibited by the myocardium during the course of a systemic disease. Many excellent reports in the recent literature, especially those of Saphir and Gore, have focused the pathologist's attention on these morphologic changes and led to the recognition that myocarditis is not rare, but, rather, occurs often during the course of many bacterial, rickettsial, viral, fungal, and parasitic diseases, and occasionally as the result of physical and metabolic changes.

This article illustrates the scope of the diseases in which myocarditis may occur by means of photomicrographs of representative lesions.

Myocarditis has been recorded in more than 50 different diseases, and these observations have been corroborated by gross and histologic demonstrations. A more careful study with multiple sections from the heart probably would reveal a larger incidence of myocarditis in many of the diseases and serve to correlate more closely the clinical signs and histologic evidence of heart involvement.

The classification for this article is based on etiology, in full realization that such a classification, while unsatisfactory for the pathologist, is valuable for the clinician. Admittedly, changes in the myocardium are often nonspecific, and diagnosis cannot be made from the morphologic picture alone, but must depend on the clinical history, bacterial cultures, agglutination tests, and other clinical laboratory procedures. Frequently, however, etiologic agents may be demonstrated in heart lesions and a specific diagnosis can be made.

In some cases the etiologic agent is unknown, and there is no associated systemic disease which could be held accountable for the myocardial lesions. This interesting group with a variable histologic pattern is classified as idiopathic myocarditis in this article.

Armed Forces Institute of Pathology, Cardiovascular Registry.

Shown as a scientific exhibit of the Section on Pathology and Physiology at the 104th Annual Meeting of the American Medical Association, Atlantic City, N. J., June 6-10, 1955.

GROUP 1.—Myocarditis Caused by Infectious Etiologic Agents.

The largest of the groups (Group 1) includes many of the common diseases. The incidence of myocarditis is greatest in this group; however, the frequency with which it occurs varies with each disease and with the amount of autopsy material available for examination.

A. Bacterial
- Lobar pneumonia
- Bronchopneumonia
- Diphtheria
- Scarlet fever
- Meningitis
- Gonorrhea
- Dysentery
- Typhoid fever
- Brucellosis
- Tularemia
- Acute nasopharyngitis and tonsillitis
- Tuberculosis
- Septicemia (Staphylococcus and Streptococcus)

B. Rickettsial
- Epidemic typhus (European)
- Epidemic murine typhus
- Scrub typhus (tsutsugamushi)
- Rocky Mountain spotted fever

C. Viral
- Rubeola
- Chickenpox
- Mumps
- Atypical pneumonia
- Poliomyelitis
- Influenza
- Guillain-Barré syndrome
- Infectious mononucleosis
- Epidemic hemorrhagic fever
- Smallpox
- Pertussis
- Yellow fever

D. Spirochetal
- Weil's disease
- Relapsing fever
- Syphilis

E. Fungal
- Actinomycosis
- Aspergillosis
- Moniliasis
- Coccidioidomycosis
- Cryptococcosis
- Mucormycosis
- North American blastomycosis

F. Protozoal and Parasitic
- Malaria
- Toxoplasmosis
- Sarcosporidiosis
- Trypanosomiasis
- Heterophydiasis
- Chagas' disease
- Leishmaniasis
- Balantidiasis
- Schistosomiasis
- Sparganosis
- Cysticercosis
- Echinococcosis
- Strongyloidiasis
- Trichinosis

GROUP 2.—Idiopathic Myocarditis
- A. Diffuse, interstitial
- B. Granulomatous myocarditis

GROUP 3.—Myocarditis Caused by Collagen Vascular Diseases
- A. Rheumatic fever
- B. Rheumatic arthritis
- C. Periarteritis nodosa
- D. Dermatomyositis
- E. Scleroderma
- F. Lupus erythromatosus

GROUP 4.—Myocarditis of Physical and Metabolic Origin
- A. Trauma
- B. Heat stroke
- C. Uremia
- D. Hypokalemia

In summary, it is believed that myocarditis is not a rare condition and is associated with a wide variety of diseases. It should be suspected and looked for in those cases which clinically manifest sinus tachycardia, abnormal rhythms, electrocardiographic changes, murmurs, fever, leucocytosis, or increased sedimentation rate during the terminal illness.

The increased clinical use of diagnostic procedures, such as frequent electrocardiograms, more bacteriological and viral studies, as well as frequent electrolyte determination during the life of the patient, coupled with the histologic examination of multiple blocks from the heart, and with a judicious use of differential stains, will add much to our knowledge of the incidence and etiology of myocarditis.

PANEL 1

Fig. 1.—Diphtheria. Subacute myocarditis in a 35-year-old white man dying of diphtheria 35 days after initial onset. Positive cultures and guinea pig inoculations. Mag. × 282. A. F. I. P. Acc. #143672.

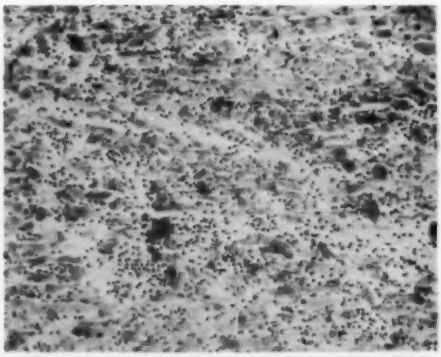


Fig. 2.—Acute nasopharyngitis and tonsillitis. Acute myocarditis in a 24-year-old white man with a history of acute nasopharyngitis and tonsillitis of four days' duration. Throat culture beta hemolytic Streptococcus. Mag. × 282. A. F. I. P. Acc. #106073.

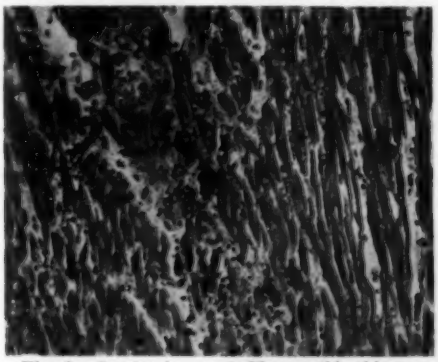


Fig. 3.—Scarlet fever. A 25-year-old white man with history of sore throat, chills, fever, and scarlatiniform rash. Death 9 days after initial onset. Blood cultures positive for a hemolytic Streptococcus. Mag. × 250. A. F. I. P. Acc. #91960.

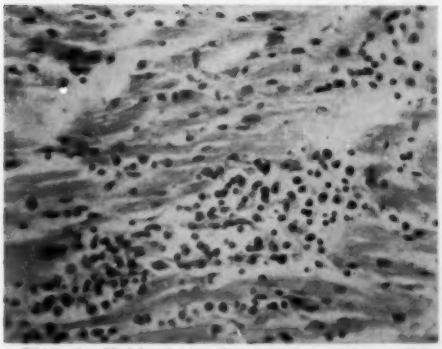


Fig. 4.—Epidemic typhus. Acute myocarditis, severe, with clinical epidemic typhus. White man, Russian. Age (?), dying of clinical epidemic typhus. Mag. × 640. A. F. I. P. Acc. #94653.

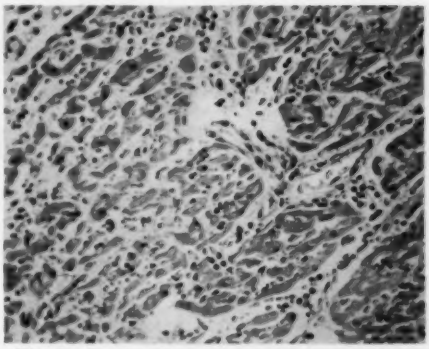


Fig. 5.—Scrub typhus. Myocarditis, acute, diffuse. A 22-year-old white male corporal with a history of fever, skin rash, lymphadenopathy, and palpable spleen of 18 days' duration; clinically, scrub typhus. Mag. × 385. A. F. I. P. Acc. #94653.

PANEL 1—Continued

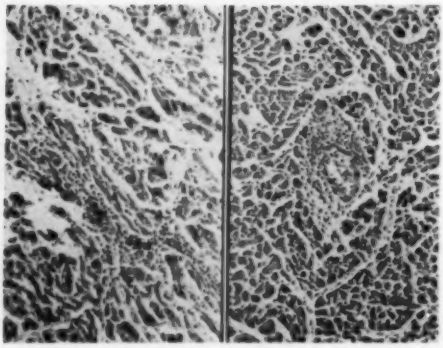


Fig. 6.—Rocky Mountain spotted fever. Focal interstitial myocarditis. A 21-year-old white man with 11-day history of clinical Rocky Mountain spotted fever. Mag. × 289. A. F. I. P. Acc. #46907.

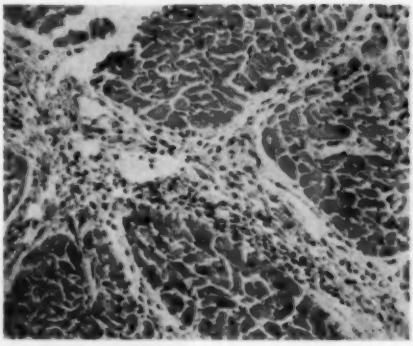


Fig. 7.—Influenza. Acute interstitial myocarditis in a 21-year-old white man with history of chills, fever, headache, nausea, vomiting, and diarrhea of 11 days' duration; clinically, influenza. Mag. × 300. A. F. I. P. Acc. #611570.

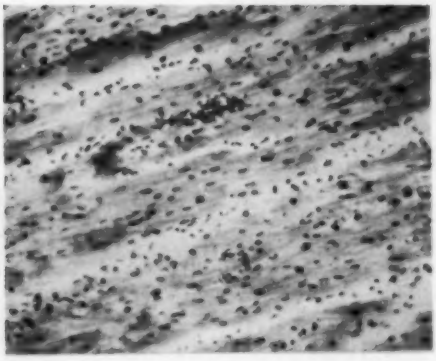


Fig. 8.—Myocarditis-poliomyelitis. Mag. × 390. A. F. I. P. Acc. #665489.

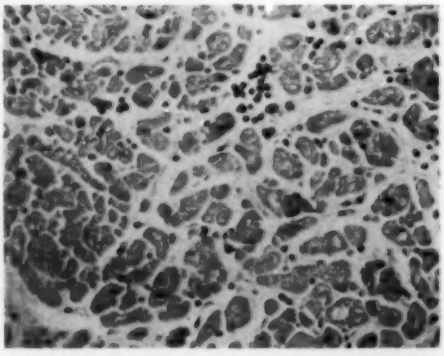


Fig. 9.—Infectious mononucleosis, myocardium. A 22-year-old white man with chief complaint of tingling, with numbness and weakness of the left arm, weakness of both legs with absent deep tendon reflexes. Heterophile 1: 5384 (absorbed). Death 6 days following admission with central nervous system involvement. Mag. × 680. A. F. I. P. Acc. #588662.

PANEL 2

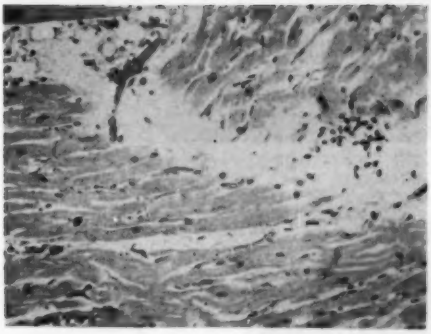


Fig. 10.—Weil's disease. Interstitial myocarditis in a 50-year-old white man with history of chills, fever, nausea, and vomiting of 10 days' duration, with positive agglutination for leptospirosis and histologically demonstrated spirochetes. Mag. × 335. Contributor: R. D. Lilly, USPH, Bethesda, Md. A. F. I. P. Acc. #99296.

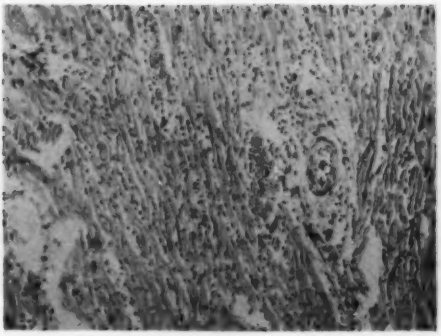


Fig. 11.—Relapsing fever. Interstitial myocarditis with overwhelming Borrelia septicemia and hepatic cirrhosis in a 40-year-old Chinese soldier. Mag. × 216. A. F. I. P. Acc. #133806.

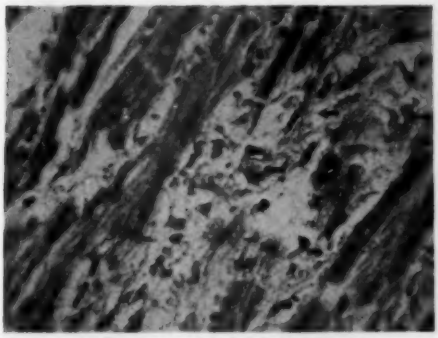


Fig. 12.—Relapsing fever (Warthin-Starry). Showing Borrelia recurrentis organisms present in myocardium. Mag. × 356. A. F. I. P. Acc. #133806.

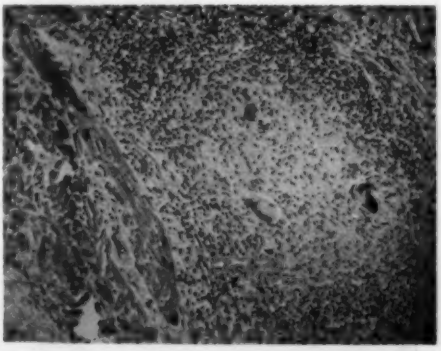


Fig. 13.—Tuberculosis. Chronic focal tuberculosis myocardium in a 35-year-old white man with 9-year history of pulmonary tuberculosis. Mag. × 240. A. F. I. P. Acc. #533380.

PANEL 2—Continued

Fig. 14.—Syphilitic gumma, heart. Age and clinical history not available.

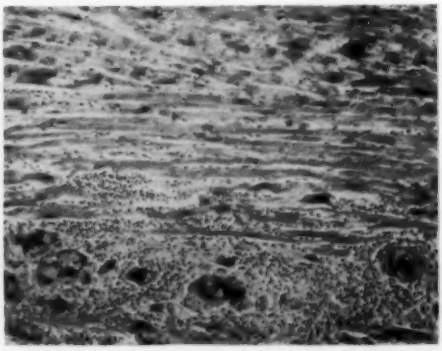


Fig. 15.—Granulomatous myocarditis. Associated with Boeck's sarcoidosis of the tracheal and bronchial lymph nodes, spleen, liver, pancreas, and kidney in a 46-year-old white man. Mag. × 300. A. F. I. P. Acc. #203191.

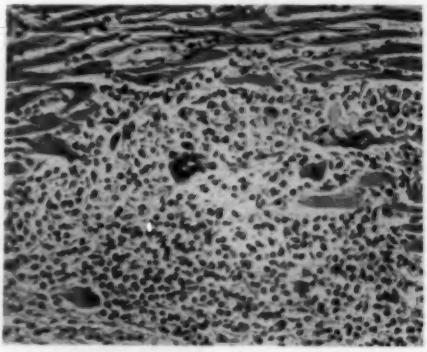


Fig. 16.—Granulomatous (isolated) myocarditis in an 18-year-old white youth with a history of swelling of the legs of one-year duration. Allergic? Mag. × 400. A. F. I. P. Acc. #313700.

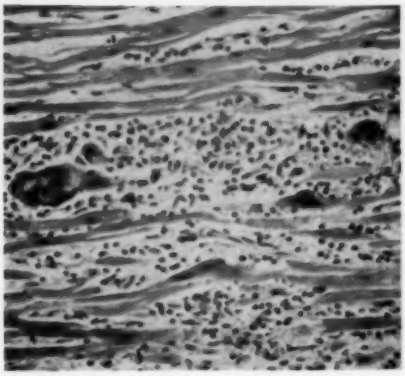


Fig. 17.—Granulomatous (isolated) myocarditis (same case). Allergic? Mag. × 400. A. F. I. P. Acc. #313700.

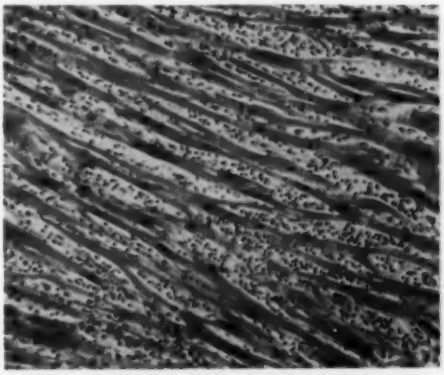


Fig. 18.—Diffuse interstitial myocarditis; idiopathic (Fiedler's). Mag. × 360. A. F. I. P. Acc. #324994.

PANEL 3

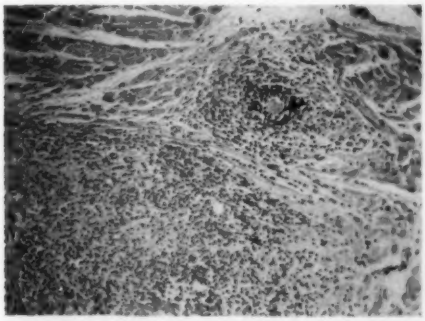


Fig. 19.—Coccidioidal granuloma of the myocardium. A. F. I. P. Acc. #114420.

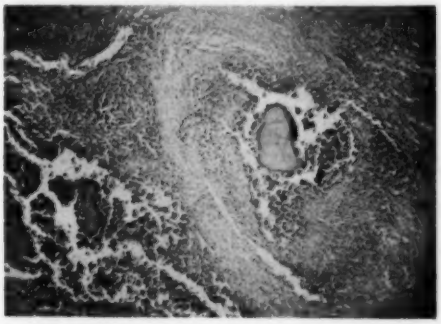


Fig. 20.—Actinomycosis, myocardium. A 30-year-old Korean man with subcutaneous abscess of breast, with extension through the chest wall involving the pericardium and myocardium. Mag. × 112. A. F. I. P. Acc. #618421.

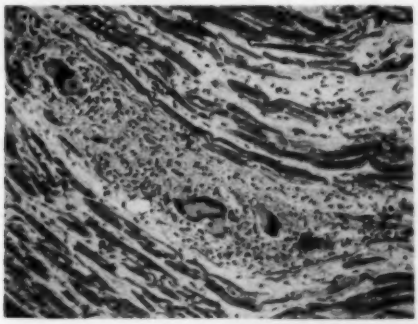


Fig. 21.—Granulomatous myocarditis in disseminated histoplasmosis. A 54-year-old white man with disseminated histoplasmosis histologically demonstrated in lungs, liver, spleen, bone marrow, kidneys, lymph nodes, stomach, and tongue. Mag. × 117. A. F. I. P. Acc. #121747.

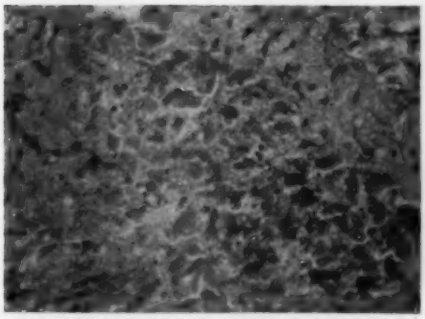


Fig. 22.—Aspergillosis, myocardium. An 18-year-old white youth with history of 6 months' fever of unknown etiology. Culture from myocardium identified as Aspergillus flavus. Mag. × 410. A. F. I. P. Acc. #659250.

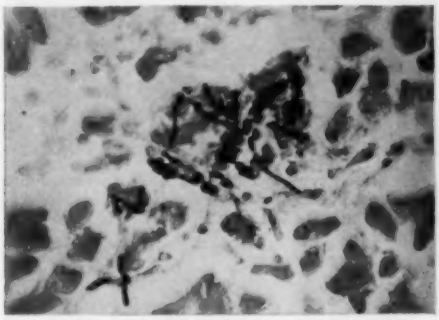


Fig. 23.—Moniliasis myocardium, Gridley's. A 21-year-old white man with extensive burns complicated by Candida septicemia and focal abscesses of brain, heart, lungs, and kidneys. Mag. × 1125 ocl. A. F. I. P. Acc. #500950.

PANEL 3—Continued

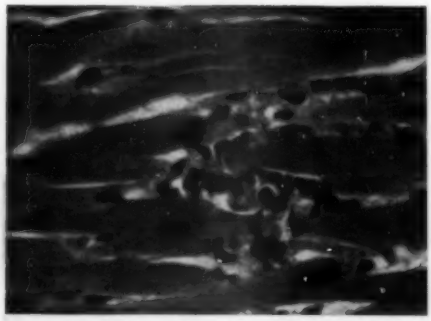


Fig. 24.—North American blastomycosis, myocardium. A 69-year-old white man with granulomatous lesions in the skin, lungs, heart, and kidneys, in which organisms histologically resembling North American blastomycosis are present. Mag. × 1500 ocl. Contributor: R. C. Dunn, M.D., Iowa Methodist Hospital, Des Moines, Iowa. A. F. I. P. Acc. #609081.

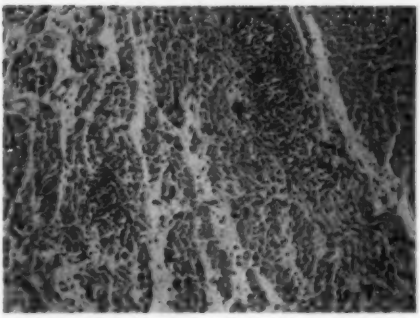


Fig. 25.—Cryptococcosis (torulosis) myocardium. A 29-year-old white man with history of retrobulbar mass, with biopsy diagnosis of malignant lymphoma. Differential on postmortem sections reveals the presence of Cryptococcus neoformans in the choroid of the eyes, lungs, liver, and heart. Mag. × 201. A. F. I. P. Acc. #262606.

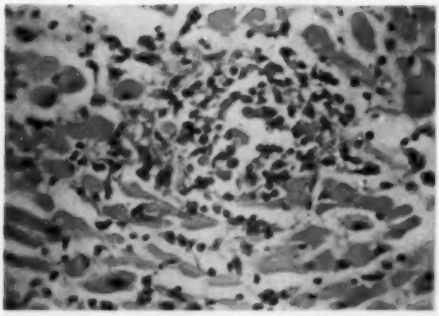


Fig. 26.—Cryptococcosis (torulosis) myocardium. Showing the etiological agent (same case). Mucicarmine; mag. × 781. A. F. I. P. Acc. #262406.

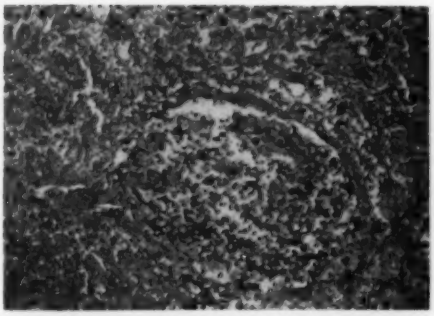


Fig. 27.—Mucormycosis myocardium. A 53-year-old Negro with an established diagnosis of multiple myeloma treated with urethan and cortisone. Postmortem examination revealed infarction of the heart due to Mucor, with similar infarcts of the lungs and kidney. Mag. × 350. A. F. I. P. Acc. #564337.

PANEL 4

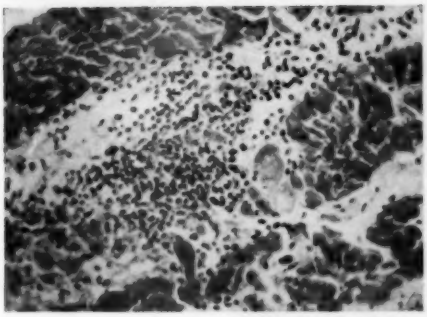


Fig. 28.—Myocarditis associated with trichinelliasis. A 22-year-old white man with chief complaints of abdominal cramp and diarrhea. History of indigestion from raw pork. Positive skin test. Trichinella larvae present in muscles and diaphragm. Death 15th hospital day. Mag. ×507. A. F. I. P. Acc. #110992.

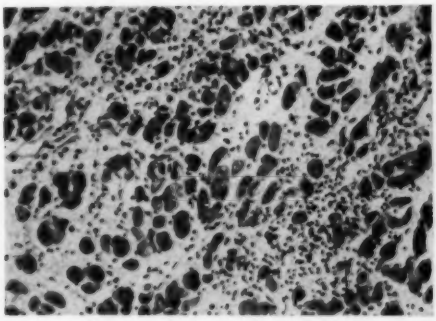


Fig. 29.—Myocarditis with schistosomiasis of liver. Clinical history not available. Mag. × 410. Contributor: Prof. Rudolph Jaffe, Caracas, Venezuela. A. F. I. P. Acc. #101272.

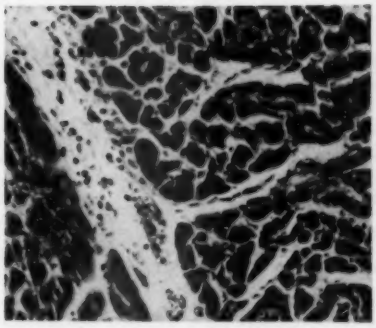


Fig. 30.—Myocardium in fatal Plasmodium falciparum infection. Clinical history not available. Mag. × 507. Contributor: Prof. Rudolph Jaffe, Caracas, Venezuela. A. F. I. P. Acc. #101272D.

Fig. 31.—Echinococcus, cyst, myocardium. A 30-year-old man with hydatid cyst of the myocardium of the right ventricle and occlusion of the left pulmonary artery by intra-arterial echinococcosis. Mag. × 88. Contributor: Dr. Daviz Mendoza, Montevideo, Uruguay. A. F. I. P. Acc. #673478.

PANEL 4—Continued

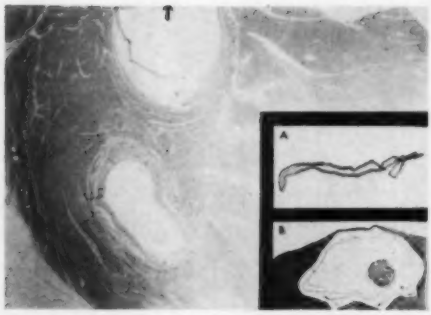


Fig. 32.—Cysticercosis myocardium. *A*, organisms from cyst of ventricle; *B*, lesion in brain with organisms. A 35-year-old Korean man, admitted to hospital because of mental confusion. Postmortem examination revealed numerous cysts of the cerebral hemisphere, the heart, and the pectoral muscles. Mag. × 13. A. F. I. P. Acc. #582814.

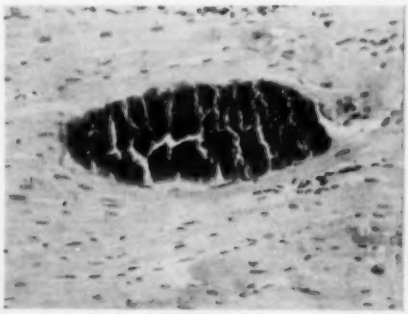


Fig. 33.—Sarcosporidiosis, myocardium (bovine). Mag. × 485. Contributor: Veterinary Pathology Section, A. F. I. P. Acc. #307887.

Fig. 34.—Toxoplasmosis, myocardium. Clinical history not available. Oil; mag. × 1050. Contributor: W. A. D. Anderson, St. Louis University, St. Louis. A. F. I. P. Acc. #97029.

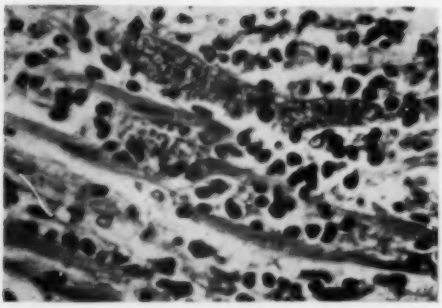


Fig. 35.—Chagas' disease, myocardium. Clinical history not available. Oil; mag. × 1350. Contributor: Dr. Hartz, San Cristobal, Venezuela, A. F. I. P. Acc. #646005.

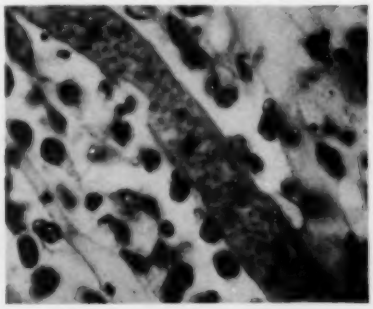


Fig. 36.—Chagas' disease, myocardium. PAS; mag. × 2300 (oil). A. F. I. P. Acc. #646005.

PANEL 5

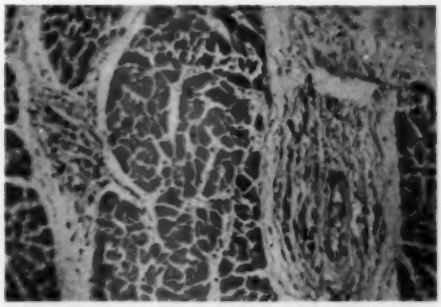


Fig. 37.—Aschoff nodule, myocardium, rheumatic heart disease. A 20-year-old white man with chief complaint of pain and swelling in both knees and pain in ankles, lower back, wrists, elbows, and shoulders. Clinically, rheumatic fever. Death 17 days after admission. Mag. × 295. A. F. I. P. Acc. #74155.

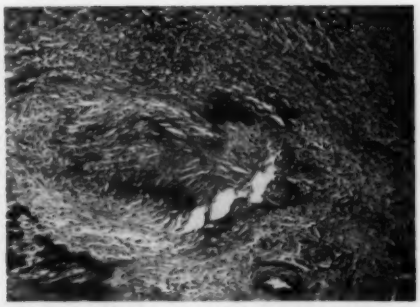


Fig. 38.—Rheumatoid nodule, myocardium. A 38-year-old white man with obvious flexion deformities of the distal phalangeal joints of hands. Similar appearance of toes with swelling. All major joints painful on motion. Many subcutaneous nodules present. Mag. × 205. A. F. I. P. Acc. #490285.

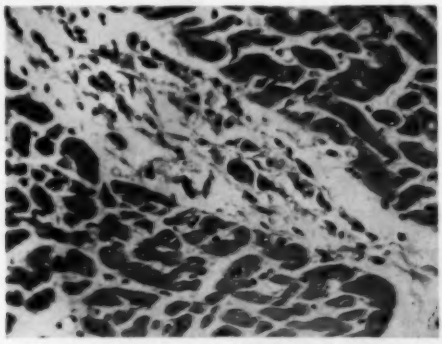


Fig. 39.—Aschoff nodule, myocardium, rheumatic heart disease. Mag. × 295. A. F. I. P. Acc. #74145.

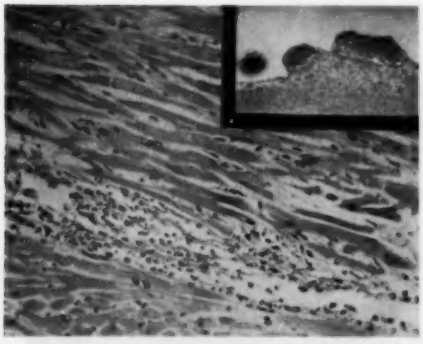


Fig. 40.—Lupus erythematosus, myocardium. Inset: Mitral valve lesion. A 21-year-old white man with history of a skin rash biopsy diagnosed as lupus erythematosus. Death 12 days after admission. Mag. × 300. A. F. I. P. Acc. #87549.

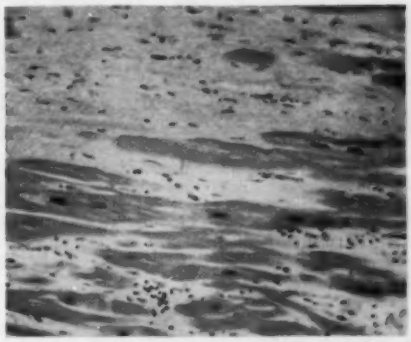


Fig. 41.—Scleroderma, myocardium. A 24-year-old white man with chief complaint of headache with pain and left facial paralysis. Skin of extremities showed fibrous thickening, characteristic of scleroderma. Death of pulmonary fibrosis and pulmonary edema. Mag. × 410. A. F. I. P. Acc. #488197.

PANEL 5—Continued

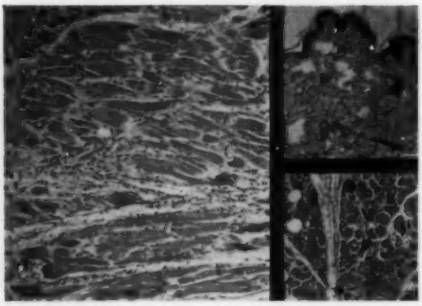


Fig. 42.—Dermatomyositis. Inset: Skin and skeletal muscle. A 58-year-old diabetic white man, with chief complaint of difficulty in walking, generalized pain, and swelling of the face, hands, and legs. Clinical diagnosis: Dermatomyositis. Mag. × 187. A. F. I. P. Acc. #507562.

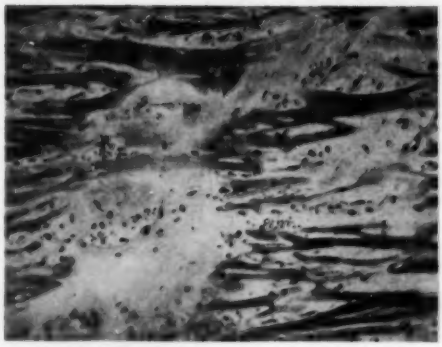


Fig. 43.—Myocardium, heat stroke. An 18-year-old white youth who collapsed following a training hike. Admitted to hospital in shock with temperature of 108.4 F. Death 16 hours after onset of symptoms. Mag. × 410. A. F. I. P. Acc. #629398.

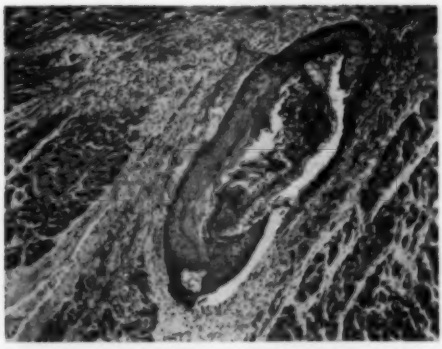


Fig. 44.—Post-traumatic myocarditis. A 74-year-old white man who developed what appeared to be a Stokes-Adams syndrome. Treated by intracardiac injection of epinephrine. Recovery, followed by death in 12 days. Surface skin carried into myocardium by needle. Mag. × 410. A. F. I. P. Acc. #591518.

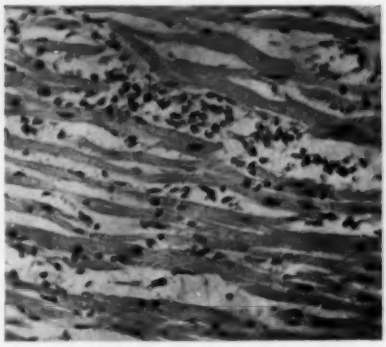
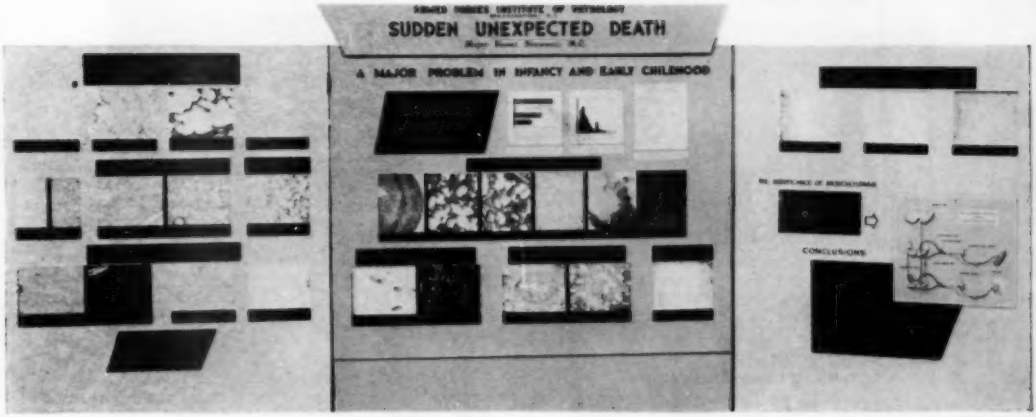


Fig. 45.—Myocarditis. Atomic bomb casualty. Mag. × 600. A. F. I. P. Acc. #259092.



SUDDEN UNEXPECTED DEATH

A Major Problem in Infancy and Early Childhood

MAJOR DANIEL STOWENS (MC), U. S. ARMY

DEATH is classified as sudden and unexpected when it occurs in ostensibly well children, without evidence of preceding disease, when the entire course of events is, apparently, instantaneous.

This entity comprises 4½% (90 cases) of the 2000 pediatric autopsies accessioned at the AFIP in the period September, 1954, to April, 1955.

It accounts for 35% of all deaths from the age of 2 months through 6 months.

It is associated with a variety of lesions, but most often no cause of death is found.

Recorded for publication Dec. 13, 1955.

Armed Forces Institute of Pathology, Washington, D. C.

Shown as a scientific exhibit of the Section on Pathology and Physiology at the 104th Annual Meeting of the American Medical Association, Atlantic City, June 6-10, 1955.

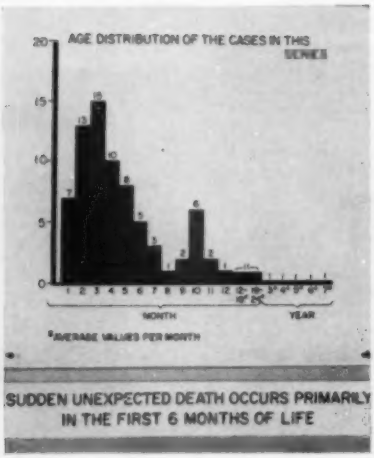


Figure 1

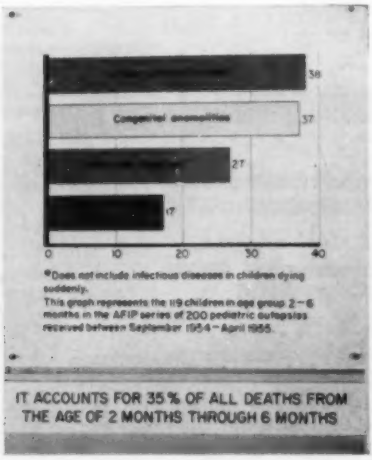


Figure 2

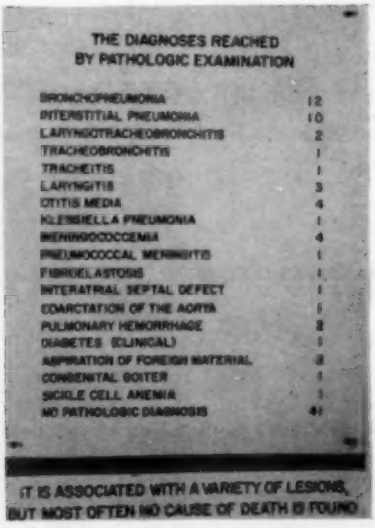


Figure 3

In 12% of the cases in this series pathologic processes of sufficient magnitude to explain death are found. Examples of these diseases are illustrated in Figures 4 to 8A.

Overwhelming sepsis is often surmised on the basis of findings such as those shown in Figures 9 and 10.

An event, probably of terminal nature, but often viewed as being of primary significance, is aspiration of foreign material.

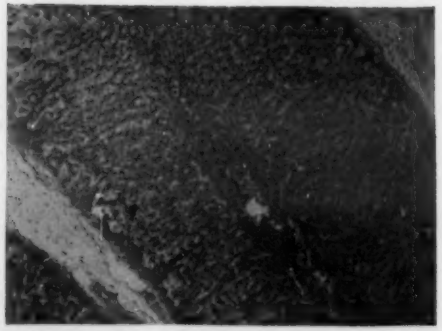


Fig. 4.—Adrenal hemorrhage accompanying meningococcemia in a 10-month-old girl. AFIP Acc. 684658; reduced from mag. × 50.

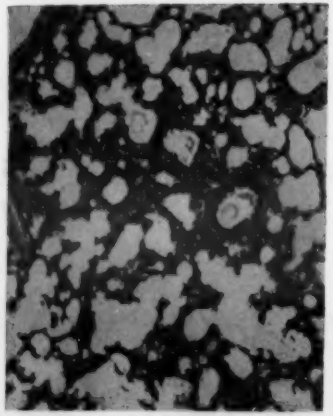


Fig. 5.—Interstitial pneumonia in a 3-month-old girl. AFIP Acc. 686471; reduced from mag. × 200.

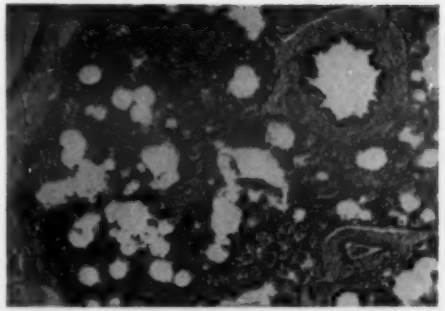


Fig. 6.—Klebsiella pneumonia in a 4-month-old boy. The intense congestion and hemorrhage seen here are characteristic of this disease. AFIP Acc. 680058; reduced from mag. × 200.

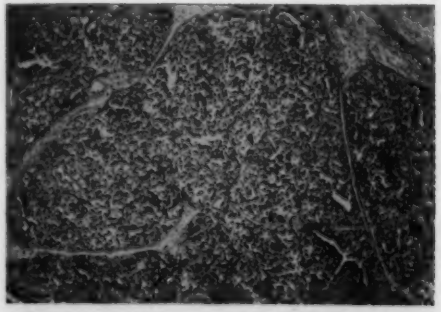


Fig. 7.—Congenital goiter in a 3½-month-old girl. Sudden death is believed to have been caused by compression of the larynx by the goiter. AFIP Acc. 683183; reduced from mag. × 330.

Fig. 8.—Peptic ulcer in a 5-day-old boy. Death resulted from exsanguinating hemorrhage. AFIP Acc. 672212; reduced from mag. × 48.

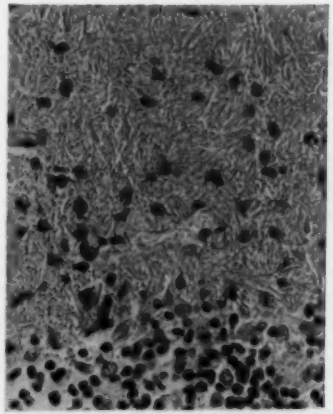


Fig. 8A.—Spleen. Sickle-cell anemia in a 15-month-old Negro girl. The child had had no previous symptoms of the disease. A severe bronchopneumonia was also found. AFIP Acc. 686730; reduced from mag. × 750.

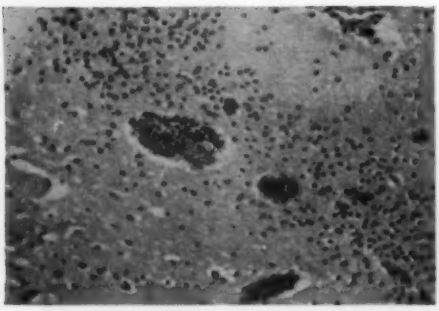


Fig. 9.—Overwhelming sepsis in a 4-month-old boy. Leucocytes in cerebral capillaries are interpreted as evidence of severe leucocytosis rather than infection of the brain. AFIP Acc. 682731; reduced from mag. ×285.

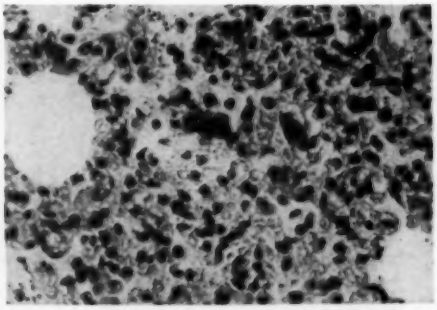


Fig. 10.—Overwhelming sepsis in a 4-month-old boy. Megakaryocytes in lung capillaries are believed to be the result of a violent response in the bone marrow to massive infection. AFIP Acc. 682731; reduced from mag. × 1680.

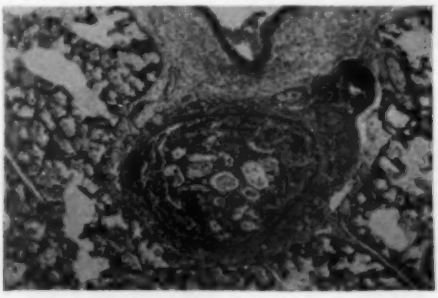


Fig. 11.—Aspiration of gastric contents in a 5-month-old girl. AFIP Acc. 680055; reduced from mag. × 190.

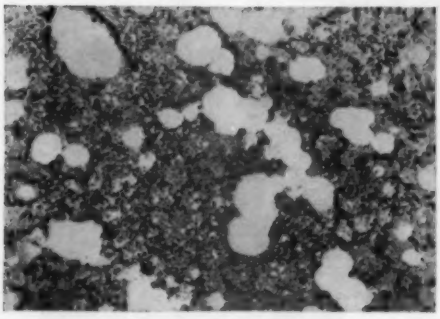


Fig. 12.—Aspiration of milk in an 18-month-old girl. The milk is the light-pink-staining material. The presence of milk in the lung is indicative of the absence of gag and cough reflexes. AFIP Acc. 681365; reduced from mag. × 160.

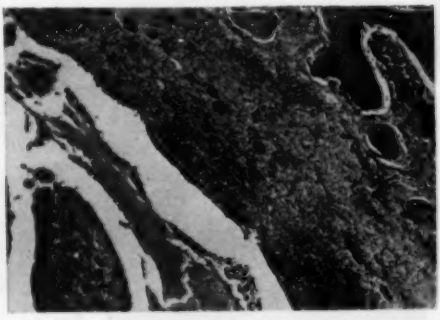


Fig. 13.—Chronic otitis media in a 4-month-old boy. AFIP Acc. 680380; reduced from mag. × 105

Purulent otitis media is commonly observed in autopsies on children. It is often the only finding, but, despite its limited nature, it is recorded as a cause of death.

In 88% of the cases in this series the findings at autopsy are insufficient to permit explanation of death on anatomic grounds. Two tissue changes common to all these cases are emphysema and pulmonary edema.

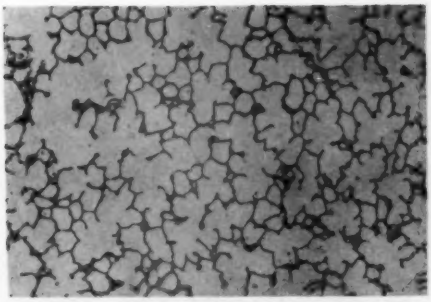


Fig. 14.—Acute emphysema in a 2-month-old girl. The degree of overexpansion of this lung is best appreciated by comparison with "normal," in Figure 18. AFIP Acc. 690425; reduced from mag. × 105.

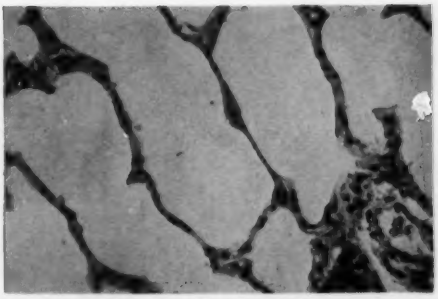


Fig. 15.—Acute emphysema in a 2-month-old girl. Stretching and thinning of the alveolar septum have obliterated the septal capillary. AFIP Acc. 690425; reduced from mag. × 430.

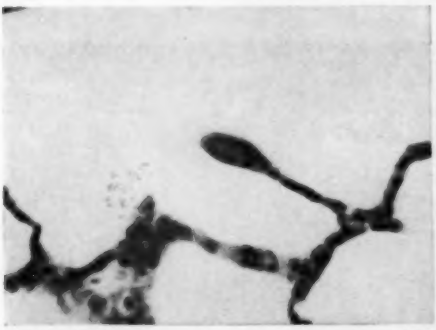


Fig. 16.—Acute emphysema in a 2-month-old girl. The knobbed appearance is characteristic of ruptured end of septum. AFIP Acc. 690425; reduced from mag. × 430.

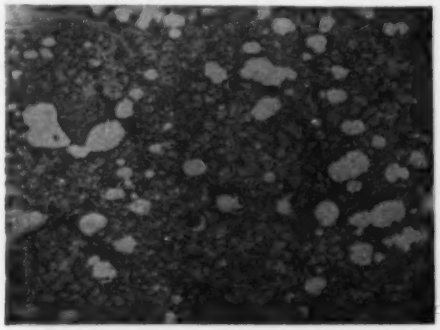


Fig. 17.—Pulmonary edema in a 4-month-old boy. Pink edema fluid nearly obscures the architecture of the lung; however, greatly distended alveoli are seen. AFIP Acc. 684665; reduced from mag. × 190.

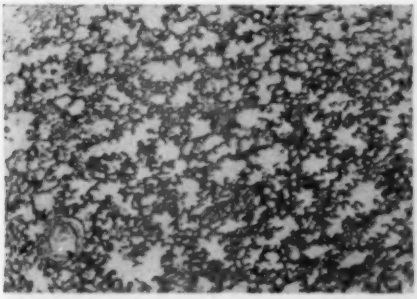


Fig. 18.—"Normal" lung in a 3-month-old boy. (This child died of the effects of congenital genitourinary anomalies.) AFIP Acc. 700015; reduced from mag. × 90.

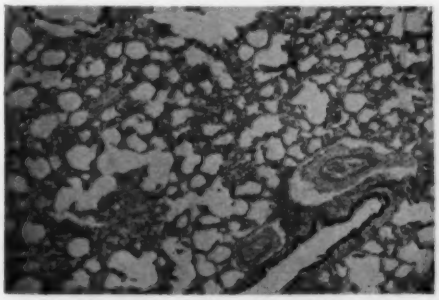


Fig. 19.—Bronchopneumonia in a 4-month-old boy. The inflammatory infiltrate is modest in amount and predominantly peribronchial in distribution, but the outstanding change is emphysema. AFIP Acc. 680496; reduced from mag. × 185.

Compare the previous figures with the examples of pneumonia in sudden death. In the lungs pictured in Figures 19 and 20, is there sufficient impairment of gaseous exchange to cause death? Is there enough evidence of the presence of bacteria to ascribe death to absorption of bacterial toxin?

The mechanism of sudden unexpected death is intimately related to the cause of acute emphysema. Acute emphysema may be produced by mechanical blockage of the airway or by bronchospasm.

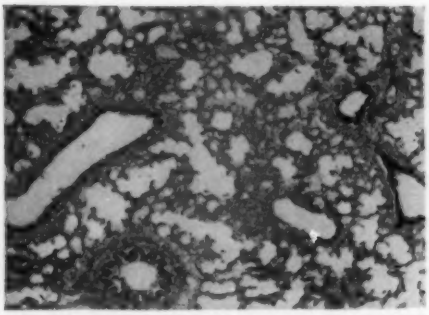


Fig. 20.—Interstitial pneumonia in a 1½-month-old boy. The inflammatory infiltrate is slight in amount and lies mainly in the alveolar septa. Most alveoli are distended, and many contain edema fluid. AFIP Acc. 688694; reduced from mag. × 205.

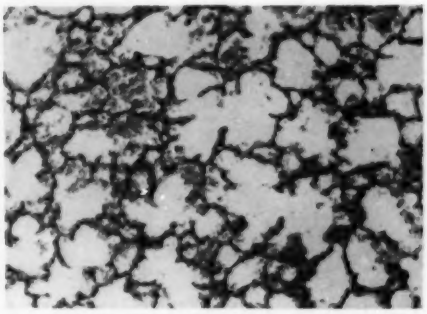


Fig. 21.—Emphysema in a 6-month-old boy. Minimal pulmonary hemorrhage is believed to follow very rapid rupture of the septa. AFIP Acc. 695545; reduced from mag. × 155.

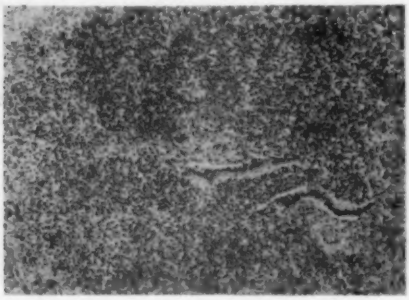


Fig. 22.—Bronchopneumonia in a 5-day-old boy. Death occurred on the fourth day of illness. AFIP Acc. 697762; reduced from mag. × 85.

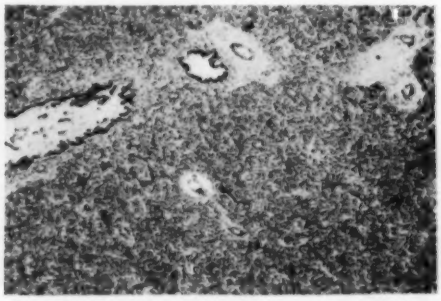


Fig. 23.—Bronchopneumonia in a 7-day-old boy. Death occurred on the second day of illness. AFIP Acc. 697299; hematoxylin and eosin; reduced from mag. × 112.

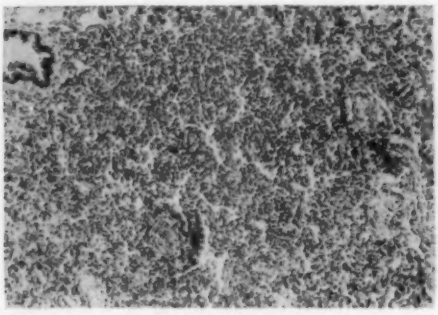


Fig. 24.—Interstitial pneumonia in a 4-month-old boy. Death occurred on the second day. The thickening of the septa is caused by an inflammatory infiltrate. AFIP Acc. 697768; hematoxylin and eosin; reduced from mag. × 170.

Fig. 25.—Organizing bronchopneumonia in a 2½-year-old girl. Death occurred on the 15th day of illness. AFIP Acc. 697973; hematoxylin and eosin; reduced from mag. × 135.

These two conditions may be present singly or together. Modest degrees of infection may also be present with these changes.

Occasionally small amounts of hemorrhage are seen.

Interstitial pneumonia, among other microscopic lesions, has been assigned as a cause of death in a great number of cases of sudden death. The appearance of unequivocally fatal pneumonia is shown in Figures 22, 23, 24, and 25.

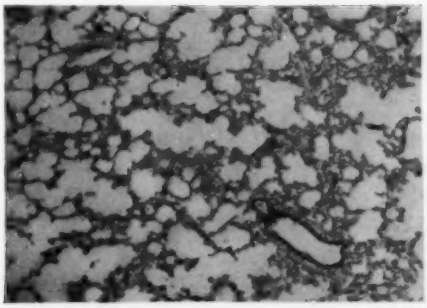


Fig. 26.—Anesthetic death in a 3-year-old boy. Instantaneous death during induction stage of open drop ether anesthesia. Severe laryngospasm was noted clinicaily. Note: No mention of resuscitative measures was made. However, dilatation of the lung when caused by overzealous artificial respiration is patchy and affects only a few alveoli and alveolar ducts. AFIP Acc. 684951; reduced from mag. × 105.

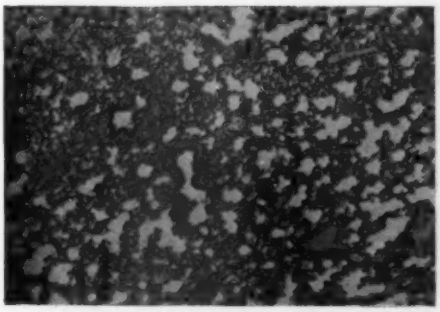


Fig. 27.—Homicidal strangulation in a girl less than one week old. The overdistention of many alveoli is partially obscured by pulmonary edema. AFIP Acc. 480497; reduced from mag. × 185.

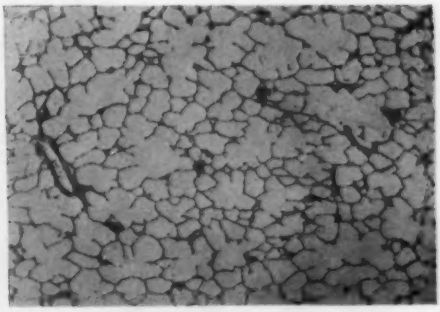


Fig. 28.—Drowning in a 5-month-old girl. The lungs contained little water, and laryngospasm was evident on gross inspection. The emphysema is comparable to that in Figure 14. AFIP Acc. 698397; reduced from mag. × 185.

The significance of bronchospasm: Clinical observations in anesthesia and research in neurophysiology indicate the existence of viscerovisceral reflexes. The pathways involved are diagrammed in Figure 29.

Conclusions: Over such pathways reflex bronchospasm is produced by lesions in distant organs.

The reflex may be elicited by many stimuli. In this series of cases 18 different anatomic lesions were found. The stimuli may be microscopic in extent, and, probably, many are sensory (e. g., temperature, pain).

The reflex affects many viscera. Only in the lungs are its effects visible. It is probably not because of its influence on the lung itself that this reflex is lethal, but because of the response of the entire cardiovascular-respiratory system.

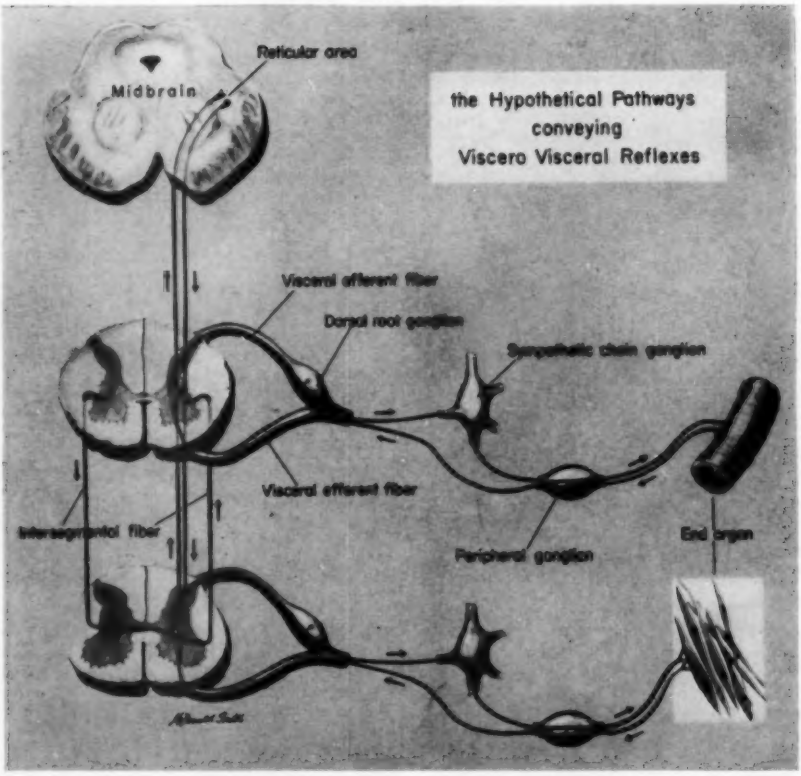

Reticular area
Midbrain
the Hypothetical Pathways
conveying
Viscero Visceral Reflexes
Visceral afferent fiber
Dorsal root ganglion
Sympathetic chain ganglion
Visceral efferent fiber
Intersegmental fiber
Peripheral ganglion
End organ

Figure 29

News and Comment

ANNOUNCEMENTS

Annual Meeting of American Public Health Association.—The 84th Annual Meeting of the American Public Health Association will be held in Convention Hall, Atlantic City, N. J., Nov. 12 to 16. Further information may be obtained from the American Public Health Association, 1790 Broadway, New York.

SHORT TRAINING COURSES OF INTEREST TO PATHOLOGISTS

Title: **Application of Histochemistry to Pathology:**

Place, duration, and dates course offered: Armed Forces Institute of Pathology, May 7-9.

Fees: None.

Admission requirements: Civilians will be accommodated as space permits.

Address inquiries to: Director, The Armed Forces Institute of Pathology, Walter Reed Army Medical Center, 6825 16th St., N. W., Washington 25, D. C.

Title: **Symposium on Cardiovascular Disease:**

Dates course could be offered: May 14-17.

Fees: None.

Admission requirements: Civilians will be accommodated as space permits.

Address inquiries to: Director, The Armed Forces Institute of Pathology, Walter Reed Army Medical Center, 6825 16th St. N. W., Washington, D. C.

Title: **Clinical Radioisotopes:**

Place, duration, and dates course offered: Vermillion, S. D.; 5 days, next course tentatively June 8-12.

Fees: Tuition, $5.

Admission requirements: Medical license.

Address inquiries to: Dr. F. E. Kelsey, University of South Dakota, School of Medicine, Vermillion, S. D.

Title: **Histochemistry:**

Place, duration, and dates course offered: University of Kansas Medical Center, Kansas City 12, Kan., June 11-23.

Fees: $30 per week.

Admission by application to: Department of Postgraduate Medical Education, University of Kansas Medical Center, Kansas City 12, Kan.

Address inquiries as above.

Title: **Mycology:**

Place, duration, and dates course offered: Month of July, at Duke University School of Medicine, Durham, N. C.

Fees: $50.

Address inquiries to: Dr. Norman F. Conant, Duke University School of Medicine, Durham, N. C.

Title: **Pathology of Obstetrics and Gynecology:**

Place, duration, and dates course offered: Free Hospital for Women, 245 Pond Ave., Brookline, Mass.; January through first half of May, one day a week (Thursday).

Fees: $150.

Admission requirements: M.D., reputable school approved by Harvard.

Address inquiries to: Assistant Dean Eugene C. Eppinger, M.D., Office for Graduates, Harvard Medical School, 25 Shattuck St., Boston 15, Mass.

Title: **Neuropathology:**

Place, duration, and dates course offered: Montefiore Hospital, Laboratory Division; January and July for three months to one year or longer.

Fees: None.

Admission requirements: Experience in general pathology of sufficient extent to qualify for Board eligibility. Some experience with clinical problems in neurology desirable.

Address inquiries to: Dr. H. M. Zimmerman, Chief, Laboratory Division, Montefiore Hospital, 210th St. and Bainbridge Ave., New York 67.

Title: **Peptic Ulcerations:** Postgraduate course sponsored by the Oklahoma Association of Pathologists, Radiologists, and College of Surgeons.

Place, duration, and dates course offered: School of Medicine, University of Oklahoma, 2 days every February (title varies from time to time).

Fees: $25.

Admission requirements: Qualified M.D.

Address inquiries to: Dr. Irvin Brown, Director, Department Postgraduate Instruction, University of Oklahoma School of Medicine, 800 N. E. 13th, Oklahoma City, Okla.

Title: **Exfoliative Cytology for Physicians:**

Place, duration, and dates course offered: University of California Medical Center, San Francisco 22; duration, variable; date arranged mutually between the University and physician. (American Cancer Society Fellowships in Exfoliative Cytology available.)

Fees: None.

Admission requirements: Preferably, certified pathologist.

Address inquiries to: David A. Wood, M.D., Director, Cancer Research Institute, University of California Medical Center, San Francisco 22.

Title: **Exfoliative Cytology for Medical Laboratory Technicians, #401:**

Place, duration, and dates course offered: University of California School of Medicine, San Francisco 22; duration 4 months; dates, Spring and Fall Semesters, commencing early in February and September of each year.

Fees: None.

Admission requirements: Registered general medical laboratory technician or equivalent.

Address inquiries to: David A. Wood, M.D., Director, Cancer Research Institute, University of California Medical Center, San Francisco 22.

Title: **Histochemical Techniques:** By Hisako O. Yokoyama.

Place, duration, and dates course offered: Pathology Department, Northwestern University Medical School; Spring Quarter.

Address inquiries to: Dr. Hisako O. Yokoyama, Pathology Department, Northwestern University Medical School, 303 E. Chicago Ave., Chicago 11.

Title: **Orthopedic Pathology:**

Place, duration, and dates course offered: Temple University School of Medicine; Tuesdays, 2 to 4 P. M., Oct. 1, 1956, through Jan. 15, 1957.

Fees: None.

Admission requirements: M.D. and an interest in bone pathology.

Address inquiries to: Dr. E. E. Aegerter, Temple University School of Medicine, 3400 N. Broad St., Philadelphia 40.

Tissue Culture Association.—The Tissue Culture Association is again sponsoring a course of instruction in the principles and techniques of cell and tissue culture. The course will be under the direction of Dr. Charles M. Pomerat, University of Texas Medical Branch. It will be given at the University of Colorado School of Medicine, Denver, from July 16 to Aug. 11. The tuition will be One Hundred Dollars.

This is an intensive four-week course dealing with the structure and function of living cells, techniques of tissue culture, and interpretation of results. It is designed to give to responsible investigators a background of general information on cultured cells and an opening wedge of training in the application of the method to problems in several current areas of research.

The morning work includes a review of the principles and techniques pertaining to the main event of the laboratory work, and a demonstration of the procedures to be used. Each participant prepares and manages his own cell cultures. Afternoons afford opportunity for library work and for consultation with the staff concerning the projects contemplated by each of the class members. Evening lectures Monday through Friday by members of the staff and by distinguished guest lecturers cover various fields of research in which the tissue culture method has been used to advantage.

The course is designed specifically for postgraduates (M.D. or Ph.D.) who plan to use cultured tissues in their research or teaching. Requests for application forms should be addressed to Dr. Mary S. Parshley, College of Physicians and Surgeons, 630 W. 168th St., New York 32, and should be completed and returned to her not later than May 1. Successful candidates will be notified about May 15.

NEW MOTION PICTURES FOR PATHOLOGISTS

Streamline Flow in Veins: Showing time 10 minutes, sound, color, 1954.

Production Data: Author: Dr. D. A. McDonald, St. Bartholomew's Hospital Medical College, London. Sponsor: Wellcome Film Unit, London.

Distribution: Committee on Medical Motion Pictures, American Medical Association, 535 N. Dearborn St., Chicago 10. Service Charge: $2.

Syphilitic Venereal Disease: Showing time 25 minutes, sound, color, 1954.

Production Data: Author: Evan W. Thomas, M.D. Producer: Sturgis Grant Productions, 322 E. 44th St., New York. Sponsor: E. R. Squibb & Sons.

Distribution: E. R. Squibb & Sons, 745 Fifth Ave., New York 22. Free loan to medical audiences.

Postmortem Tissue Donation: Showing time 24 minutes, sound, color, 1954.

Production Data: Author: National Naval Medical Center. Producer: Byron, Inc., 1226 Wisconsin Ave., N.W., Washington 7, D. C. Sponsor: National Selected Morticians.

Distribution: National Selected Morticians, 1616 Central Ave., Evanston, Ill. Free loan.

Chemotherapy: A Research Frontier: Showing time 60 minutes, sound, color, 1954 (T.V. Kinescope).

Production Data: Scientific Producers: Sloan Kettering Institute for Cancer Research. Producer: American Cancer Society, 47 Beaver St., New York 4.

Distribution: Burroughs Wellcome & Co., Tackhoe 7, N. Y. Free loan.

Nephrosis in Children: Showing time 18 minutes, sound, color, 1954.

Production Data: Scientific Advisor: Robert E. Cooke, M.D., Yale University. Sponsor: Charles Pfizer & Co., Inc., for National Nephrosis Foundation.

Distribution: Film Library, Pfizer Laboratories, 630 Flushing Ave., Brooklyn 6, N. Y. Loan.

Dynamics of the Tubercle: Showing time 30 minutes, sound, color, 1956.

Production Data. Authors: Robert H. Ebert, M.D.; William R. Barclay, M.D. University of Chicago. Producers: David S. Ruhe, M.D., University of Kansas and Churchill-Wexler Productions, Inc. Sponsor: Pfizer Laboratories.

Distribution: Charles Pfizer & Co., Inc., 630 Flushing Ave., Brooklyn, N. Y. Loan.

Principles of Respiratory Mechanics (Part I): Showing time 22 minutes, sound, color, 1954.

Production Data: Scientific Producer: Department of Physiology, Harvard School of Public Health. Sponsor: National Foundation for Infantile Paralysis, 120 Broadway, N. Y.

Distribution: Modern Talking Picture Service, Inc., 45 Rockefeller Plaza, N. Y. Service Charge: $1.

Books

BOOKS RECEIVED

Microbiology: An Introduction. By Ernest A. Gray, M.Sc., M.R.C.V.S., Chief Bacteriologist, Bayer's Biological Institute, Exning, England. Price, $3.75. Pp. 175, with 25 illustrations. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1955.

Tuberculosis and Aspiration Liver Biopsy: Its Clinical Significance in Diagnosis and Therapy. By A. J. Ch. Haex, M.D., Head of the Department of Gastroenterology, and Cornelia van Beek, former instructor in Pathology, Rijksuniversiteit, Leiden. Price, 15.00 francs. Pp. 100. De Erven F. Bohn, N.V., Frankestraat 42, Haarlem, The Netherlands, 1955.

BOOK REVIEWS

Lehrbuch der speziellen pathologischen Anatomie. Volume 1, Part 5. By Dr. Eduard Kaufmann; edited by Prof. Dr. Martin Staemmler. Pp. 140. Walter de Gruyter & Co., Genthinerstrasse 13, Berlin W 35, 1955.

This book, the fifth part of the first volume of the "New Kaufmann," deals with the endocrine glands. It is written by E. Tonutti and is an extended treatise on the gross and microscopic appearance of these organs and on their normal functions. The histochemistry of the various pertinent cell structures as well as the various hormones of the glands, their interrelationship, and what is justly named "histophysiology" are taken up. Certain anatomic changes occurring in hyperactive glands and in instances of involution are described in detail. However, neither gross nor microscopic abnormalities are discussed, and disease entities occurring in any one of these organs are disregarded. In other words, this treatise is definitely not a pathologic anatomy but rather a volume of normal histology and physiology. The reviewer takes it for granted that in another volume the pathology of the endocrine glands will also be the topic of discussion and that this part serves merely as an introduction and background for what will have to come later; otherwise, something is woefully lacking. However, it would be far better if the diseases of each of the endocrines were taken up immediately following the discourse on the physiology of the pertinent gland.

As this chapter stands, it is excellent. It is clear-cut, and the large number of subheadings makes it readable and helpful in the finding of pertinent topics. Even though this volume does not give any pathology, it is of great value in finding a concise and up-to-date discussion of the normal physiology and, as is so important for the pathologist, the interrelationship of the endocrines and the effect of different hormones on various structures. Thus, in the chapter on androgens, their effect upon structure and function of the male genital tract is taken up first. This is followed by a discussion of their effect upon the metabolism, the skeleton, musculature, and integument. Last, their influence upon the female organism is explained. Only the islet apparatus of the pancreas is presented with a good review of the various cells of the islets, the localization of insulin and also of glycogen production. Experimental observations on the status of the alpha and beta cells in the hypophyseal, thyroidal, steroid, and alloxan diabetes are illuminating. There is an abundance of references to the more recent literature.

This volume is indispensable to the pathologist as an excellent background for endocrine disturbances, not in the sense of providing a treatise on changes of diseased organs, but on the normal physiology and the interrelationship of the endocrine glands. In this field it provides something which is not found in other texts on pathology.

Clinical Disorders of Hydration and Acid-Base Equilibrium. By Louis G. Welt, M.D. Price, $6.00. Pp. 262, with 11 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1955.

This book considers the pathogenesis and treatment of disorders of fluid and electrolyte metabolism. The first part includes physiologic considerations, such as the volume and composition of body fluids, the internal exchange of water and electrolytes, and the extrarenal exchange of the same. There is a readable chapter on acid-base relationships, a section on renal physiology.

and finally one on the consequences of expansion and contraction of the body fluids. The second part includes clinical considerations. There are several chapters on the maintenance requirements, the use of parenteral fluids, and a detailed discussion of dehydration with specific clinical examples. There are separate chapters on the disorders of acid-base equilibrium, the pathogenesis and management of edema, and acute renal insufficiency.

The material is developed in a straightforward readable manner by a man with extensive experience in this field. The discussions are amplified by the presentation of clinical examples. Where judgment is made of several conflicting theories, the choice is clearly indicated and adequate references are given. This book will be a worth-while addition to the reading list of all those concerned with understanding and treating problems of salt and water balance.

The Lung: Clinical Physiology and Pulmonary Function Tests. By J. H. Comroe Jr., R. E. Forster, A. B. Dubois, W. A. Briscoe, and E. Carlsen. Price, $5.50. Pp. 219, with 56 illustrations. The Yearbook Publishers, Inc., 200 E. Illinois St., Chicago 11, 1955.

This book is an attempt to present in a form understandable to all physicians and medical students the complexities of modern pulmonary function tests. Within the confines of this small volume has been compressed a large amount of information. On the whole the explanations, the figures, and charts are clear and understandable. The text discusses lung volumes, ventilation, pulmonary circulation/ventilation ratios, diffusion of oxygen and carbon dioxide in the lung, and the mechanics of breathing. The bibliography is limited to a few selected references in each area. The book will be of help and interest to those pathologists who may be faced with, and interested in the interpretation of, the data of modern pulmonary function measurements and their correlation with structural changes.

Differential Diagnosis: The Interpretation of Clinical Evidence. By A. McGehee Harvey, M.D., and James Bordley III, M.D. Price, $11.00. Pp. 665. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1955.

This book presents in an attractive way modern concepts and methods of differential diagnosis, with particular emphasis on the interpretation of clinical evidence. The material is selected largely from clinical-pathological conferences given particularly at the Johns Hopkins Medical School. A few cases are taken from material presented at the Mary Imogene Bassett Hospital in Cooperstown, N. Y. The idea represents the thinking of many individuals, summarized and interpreted by the authors. The general scheme is to present clinical problems on the basis of principal signs or symptoms, to discuss the differential diagnosis, and then, by means of illustrative cases, to present the necropsy findings. Thirty tables are included to facilitate consideration of the type of diseases to be considered for each set of signs and symptoms, including laboratory findings. An excellent index makes the use of the material easy. The various chapters deal with such problems as aortic insufficiency, heart failure, pain in the chest, sudden death, failure of urinary excretion, hematemesis and melena, jaundice, hepatomegaly and ascites, lymphadenopathy and splenomegaly, fever of obscure origin, diseases involving the lungs or mediastinum, meningitis, special diagnostic problems, including the diagnosis of certain rare diseases, and finally a series of eleven unknown cases for study, in which the reader can attempt to make the diagnosis. In the introductory chapter, the authors discuss the problems of definition and the methods of approach to diagnosis of disease. Their effort is to present the subject as a "systematized discipline, . . . by marshalling all the facts, then proceeding with an unprejudiced analysis of the facts, and ending with a logical conclusion." Their purpose is to analyze the problem of differential diagnosis through observation of both the successes and failures of experienced diagnosticians. They emphasize, also, the importance of having the cases selected to illustrate important problems rather than merely to trip up the analyst.

Although the authors state that it is not their intention to present this material as a textbook, there is no doubt that it will be a very stimulating book for interns, residents, young physicians, and medical students. It should also be of considerable value to pathologists.

The Relief of Symptoms. By Walter Modell, M.D., F.A.C.P. Price, $8.00. Pp. 450. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1955.

A superbly written book which vividly and interestingly brings forth the main purpose of a physician in clinical medicine: the relief of distress in the sick. At a time when medicine places the main emphasis on the cure of the disease, undoubtedly as a result of the advances in specific

therapeutic agents, it is most welcome to be presented with a work where treatment is directed entirely to the patient and his comfort.

The book is divided into three parts. The first five chapters deal with general considerations in the importance of relief of symptoms; what makes a symptom, later translated to the physician as a complaint; what degree of relief should the physician consider the proper goal to attain, and a general discussion on therapeutic trials and the analysis of the response achieved. The chapter in this section dealing with the placebo action of drugs and physician is outstanding. The second part of the book deals with relief of specific symptoms, and the author dedicates a chapter to each of twenty-four of the common symptoms which induce the patient to seek medical attention. Each symptom is discussed from the point of view of the clinical problem, the etiology, the problem of relief, and a comprehensive, up-to-date discussion of the available therapeutic measures for relief. In the chapter dedicated to edema, for instance, there is an excellent discussion of therapy for congestive heart failure.

The third part consists of the last chapter which is dedicated to cortisone and corticotropin, their indications for use, and the potential harmful effects of their indiscriminate use for the relief of symptoms.

This book should be invaluable reading for the medical student and every physician dedicated to the practice of medicine.

Atlas of Congenital Anomalies of the Heart and Great Vessels. By Jesse E. Edwards, and others. Price, $13.50. Pp. 202, with 256 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1954.

The Atlas contains, with minor exceptions, the material presented in "Congenital Anomalies of the Heart and Great Vessels" (T. J. Dry, and others, Charles C Thomas, Publisher, Springfield, Ill., 1948), which was a clinicopathologic study of one hundred thirty-two cases. Additional cases have been added to the Atlas, and many of the case studies have been expanded to include data obtained by techniques such as cardiac catheterization, oximetry, dye-dilution methods, and intra-arterial pressure studies. The bibliography has been greatly expanded. The case presentations are brief and concise; the pictorial material is beautifully presented. Pathologists will find this Atlas a very useful reference.

Tumors of the Major Salivary Glands. By Frank W. Foote Jr., M.D., and Edgar L. Frazell, M.D. Price, $1.50. Pp. 149, with 184 illustrations and 2 color plates. Armed Forces Institute of Pathology, Washington 25, D. C., 1954.

The presentation in this monograph is a straightforward discussion of what has tended to be a confused group of tumors. Much of this confusion has arisen from the obscure origins of many of these tumors which has in turn been reflected in much of the difficulty in classifications. The authors circumvent this problem by presenting a straight morphological classification and limit the discussion of origin to a single paragraph for each tumor. This approach detracts in no way from the value of the fascicle. The discussion of mixed tumors makes up the largest single section, and both benign and malignant forms are considered. The illustrations of malignant mixed tumors show particularly well the varied patterns often seen in these tumors. Mucoepidermoid tumors are subdivided into low-grade and high-grade which, while perhaps serving a limited practical purpose, does not seem to be fully satisfactory in view of the many transition forms often shown by this tumor.

Adenoid cystic carcinomas are well considered and particularly well illustrated. The well-known pattern of squamous-cell carcinomas leads the authors to dismiss these tumors with only superficial consideration. Papillary cystadenoma lymphomatosum, oxyphile-cell adenoma, and benign lymphoepithelial lesions complete the monograph. The authors question the terminology of the last lesion, for they feel it is neoplastic and not necessarily benign. It is fortunate that they have included a discussion of this recently recognized pathologic entity.

Tumors of the Retroperitoneum Mesentery and Peritoneum. By Lauren V. Ackerman, M.D. Price, $1.50. Pp. 136, with 105 illustrations. Armed Forces Institute of Pathology, Washington 25, D. C., 1954.

Originally planned as two fascicles, Dr. Ackerman has combined these tumors into a single monograph comprising a portion of the "Atlas of Tumor Pathology." That interesting and hitherto poorly defined group of tumors found in the retroperitoneal space makes up the first

portion of the fascicle. Adequate classification of these diverse tumors has never been satisfactorily accomplished. Ackerman offers a straightforward and disarmingly simple classification and considers in turn mesodermal, neurogenous, renal, embryonic, and metastatic origins. Mesodermal tumors, of course, make up the bulk of the group, and both benign and malignant types of the respective tumors are discussed. Neurogenous tumors include those arising from nerve sheaths as well as those from the sympathetic chain. While tumors arising from heterotopic adrenal tissue and paraganglion tumors are discussed, pheochromocytomas are only briefly mentioned. Tumors of the mesentery include the benign lymphangiomas, lipomas, and leiomyomas, and the malignant liposarcomas and fibrosarcomas. The primary peritoneal tumor is mesothelioma, and the discussion and illustrations of these are excellent. The section concludes with a consideration of metastatic tumors.

This fascicle continues in the same excellent pattern which has been established throughout the series. The text, which in some areas is sketchy, is more than adequate. In addition to his own wide experience, the author refers repeatedly to the extensive work of Arthur Purdy Stout in this field. The illustrations are, of course, excellent.

Tumors of the Stomach. By Arthur Purdy Stout, M.D. Price, $1.75. Pp. 104, with 66 illustrations and 5 colored plates. Armed Forces Institute of Pathology, Washington 25, D. C., 1953.

It is fortunate that Arthur Purdy Stout consented to write this fascicle of the "Atlas of Tumor Pathology." His perspective in the field is readily apparent in the Introduction, where he explains the seemingly disproportionate space in this fascicle devoted to unusual tumors. Here, too, Dr. Stout permits himself some speculation on the origins of gastric carcinomas, considering particularly the roles of atrophic gastritis and peptic ulcer. Though benign gastric tumors constituted only seventeen per cent of the tumors making up the series of six hundred fifty-one gastric tumors seen at Columbia University in a forty-two year period, almost half of the monograph is concerned with these tumors. Here polyps, heterotopic tumors, and leiomyomas are extensively discussed and well illustrated. The rarer tumors such as hemangiopericytoma, glomus tumor, lipoma, neuroma, and neurilemmoma are also considered.

While benign tumors are thoroughly covered in this monograph, the treatment of carcinoma is no less complete, and here Dr. Stout discusses in some detail the various types of spread shown by gastric carcinomas. In this discussion those tumors that are grossly so far-advanced as to prevent gross identification as to method of growth are grouped into a class of "no special type"; thirty-seven per cent of the cases were so classified. While such classification destroys some of the over-all value of the system, it probably is a necessary expedient.

In addition to carcinomas, lymphoid and reticuloendothelial tumors are thoroughly discussed. Sarcomas, particularly fibrosarcoma, are considered; and the monograph concludes with a brief discussion of treatment, since treatment is so often influenced by the pathology of the tumors.

A Textbook of Medicine. Edited by Russell L. Cecil, M.D., Sc.D., and Robert F. Loeb, M.D., Sc.D. Ninth edition. Price, $15.00. Pp. 1786, with 201 illustrations. W. B. Saunders Company, 218 Washington Sq., Philadelphia 5, 1955.

The ninth edition of this deservedly popular Textbook of Medicine, appearing four years after the eighth edition, has grown to the extent of an additional 159 pages and now is a tome of 1786 pages. Obviously a critical review is unnecessary. No doubt the editors and publishers, alike, are keenly aware of the problem of presenting a one-volume textbook of medicine and at the same time holding down its weight correspondingly. To this reviewer it is reminiscent of the well-known song in "Oklahoma" to the effect that "they have gone about as far as they can go." In this new edition thirty-nine new subjects have been covered which were not discussed in previous editions, and, because of deaths and editorial changes, fifty-eight new treatises have been prepared. As in the past, the emphasis is on physiology and biochemistry, and the arrangement is to include these aspects, together with the descriptions of the diseases. Practically all of the contributors are well known in relation to the subjects they have discussed, and following most of the discussions are references to enable students to pursue the material further. The Tables at the end of the book dealing with normal laboratory values of clinical importance will continue to be of value, particularly, to medical students. The Index has been unusually well prepared, and it covers practically ninty-seven pages of fine print. The problem of size and of multiple authorship is illustrated in this edition in the consideration of the three diseases, tuberculosis,

syphilis, and pneumococcal pneumonia. Practically one hundred pages are devoted to these three infectious diseases. In view of the rapid changes in these diseases it will be interesting to see how the problem of revision is handled with respect to them in the next edition. Obviously, as patterns of disease continue to change under the impact of changing therapies, allowances for these will be necessary in all textbooks in the medical field. Regardless of these difficult problems, however, this textbook will continue to serve as an unusually useful source of information for medical students and younger physicians. It might be added that the printing and illustrative material continue to be of the high quality characteristic of the products of W. B. Saunders Company.

Physical Techniques in Biological Research. Vol. 1. By Gerald Oster and Arthur W. Pollister. Price, $13.50. Pp. 564. Academic Press Inc., 125 E. 23d St., New York 10, 1955.

Rapid advance in the application of new physical techniques to biological problems has occurred in recent years. The first volume of a multi-authored series is an up-to-date presentation of the principles and practice of modern optical techniques as applied to problems of cell structure. It contains nine chapters dealing with the following subjects: Photochemistry and Luminescence; Light Scattering; Absorption Spectroscopy; Ultraviolet Absorption Spectrophotometry; Infrared Spectrophotometry; The Light Microscope; Phase and Interference Microscopy; Birefringence and Dichroism; Electron Microscopy. Each chapter is written by an expert in the area. The chapters are divided into discussion of the theoretical foundation of the method and the instrumentation and technical problems of the application. The theoretical portions are written in an understandable and usually clear fashion without too great oversimplification. The illustrations, both figures and photographs, are clear. The editors and contributors are to be congratulated on the whole for their excellent job. This book could well be a part of the laboratory equipment of the modern microscopist, the clinical pathologist who uses light absorption techniques of qualitative and quantitative analysis, and the investigator in pathology.

Classics of Biology. By August Pi Suñer, translated by Charles M. Stern. Price, $7.50. Pp. 337. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1955.

The book consists of sixteen chapters which range broadly over biology. Some of the titles are: Matter and Energy in Life, Cell Theory, Stimulus and Excitation, Biocatalysts, Metabolism, Growth and Reproduction, Form and Dynamics of Reproduction, Heredity, Life on Earth, Causation and Design, Reflexes, Consciousness and Will, The Whole and Its Parts. Each chapter consists of a sophisticated historical résumé of the subject, followed by a number of historical quotations in English, which are one to five pages long.

The historical summaries are clear and frequently stimulating. The selection of original sources is particularly refreshing, as many of them are from languages other than the English, French, and German, with which we are familiar. The translation of the original Spanish text and of the non-English sources are excellent. There is an index of authors quoted, and another of subjects and names.

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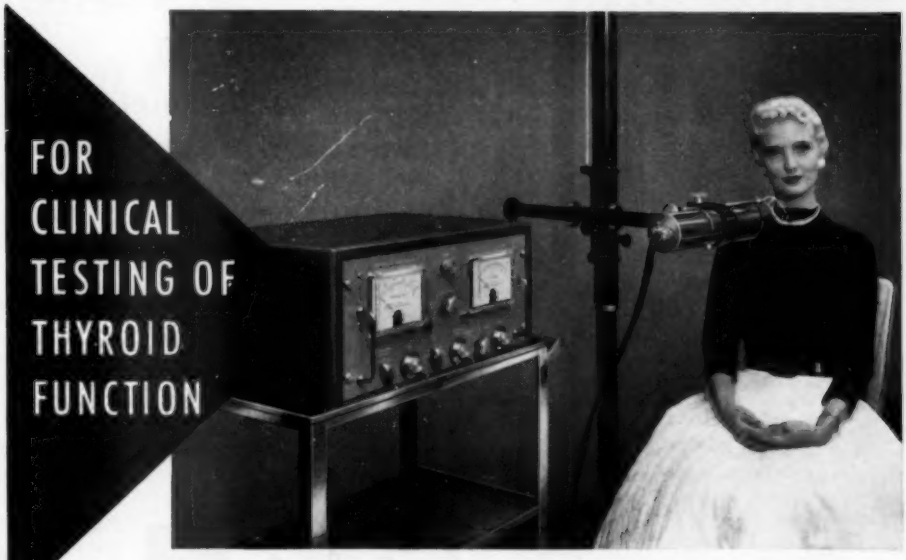

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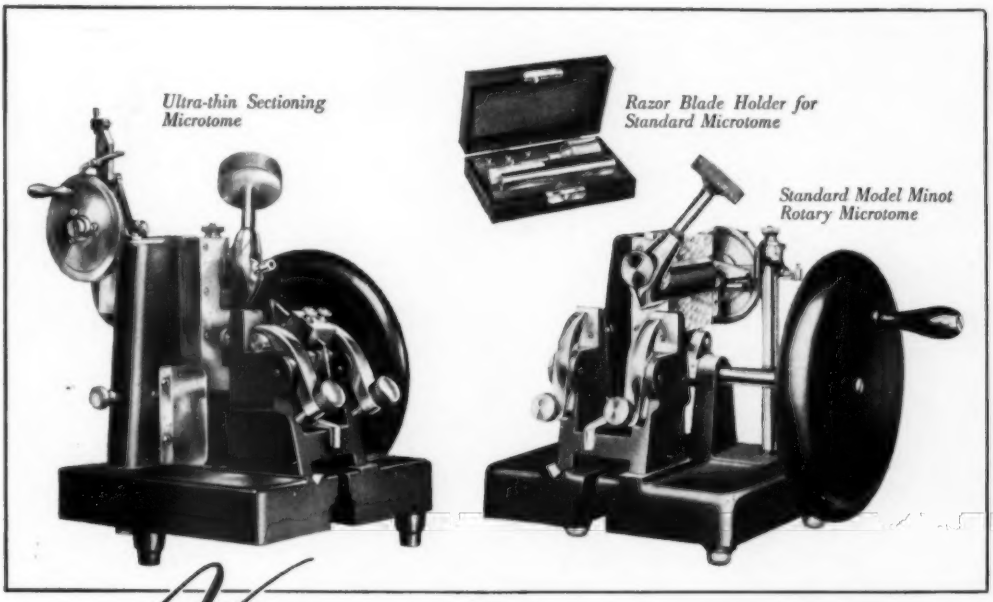

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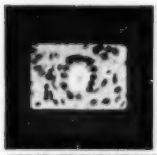

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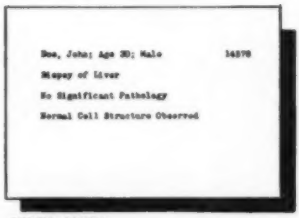

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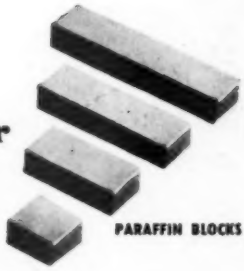

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